

DESCRIPTION

PREVENTIVE AND/OR THERAPEUTIC AGENT FOR DISEASE
IN WHICH MITOCHONDRIAL BENZODIAZEPINE RECEPTOR PARTICIPATES

5 Technical field

The present invention relates to a preventive and/or therapeutic agent for a mitochondrial benzodiazepine receptor mediated disease comprising nitrogen-containing heterocyclic compounds as an active ingredient.

10 Background art

In 1977, mitochondrial benzodiazepine receptor (hereinafter, it is abbreviated as MBR.) was identified as a receptor that is different from a benzodiazepine binding site in GABA_A receptor to which benzodiazepines bind ("Science, 198, 849-851 (1977)", "Proc. Natl. Acad. Sci., 89, 3805-3809 (1977)"). Though its physiological function is not necessarily clarified, it has been reported to get involved in steroid synthesis, the differentiation and proliferation of cells, and the immune function modulation, etc. In peripheral tissue, there are MBRs in immune system cells such as red blood cell, platelet, monocyte, and macrophages besides adrenal cortex, heart, smooth muscle, kidney, lung, testis, and in central nervous system in plexus chorioideus, corpus pineale, olfactory bulb, cerebral cortex, and hippocampus, etc. Cells expressing MBRs in central nervous system have mainly been known to glial cells. They have been used as a marker of gliosis so that the MBR expression level increases along with the neurodegenerative disease such as Alzheimer's disease, cerebral ischemia, multiple sclerosis, and Huntington's disease, etc.

There are MBRs in mitochondrial outer membrane, which transport cholesterol from intracellular to the internal membrane of mitochondria that is the active site of P-450_{scc}. Steroid synthesized in the brain is called as neurosteroid. Cholesterol, which is the steroid precursor, is converted into pregnenolone metabolized with side-chain cleavage enzyme P-450_{scc}. This process is the first process of steroid production system. However, it has been indicated that this transport process was the rate-determining process in steroid production system rather than metabolism with P-450_{scc}. It has been thought that the neurosteroid content in the brain could be adjusted if the function of MBRs could be regulated. Actually, it has been reported that a diazepam binding inhibitor (hereinafter, it may be abbreviated as DBI.), which was identified as an endogenous ligand of a benzodiazepine binding site in GABA_A receptor

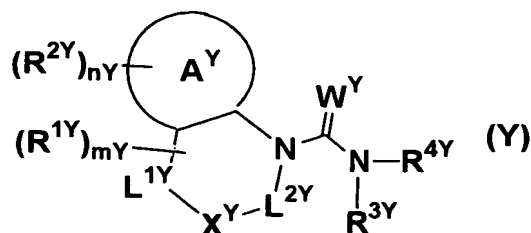
and MBRs, promoted the pregnenolone synthesis at mitochondrial fraction derived from rat brain and glioma cells.

It has been reported that DBI content in hippocampus increased by loading sound stressor to rat and DBI concentration in cerebrospinal fluid of patients with depressed mode rose. Therefore, it is expected that the amount of neurosteroid production can increase under stress condition. As experiment results supporting this, it has been reported that the various neurosteroid content in the brain increased by loading stressors to rats, such as forced swimming, foot shock, carbon dioxide exposure and constraint and so on.

Neurosteroids regulate the function of various receptors and ion channels positively or negatively according to the types thereof. For example, though pregnenolone sulfate and dehydroepiandrosterone sulfate control the function of GABA_A receptor, progesterone, allopregnenolone and tetrahydrocorticosterone activate it. In addition, though pregnenolone sulfate also controls the function of AMPA/kainate-type glutamate receptor, glycine receptor, and voltage-dependent calcium channel, activates NMDA-type glutamate receptor. Additionally, progesterone controls the function of acetylcholine receptor as well as glycine receptor. Further, though dehydroepiandrosterone sulfate activates the function of σ receptor, progesterone control adversely. Thus, it has been thought that as a result of balance between an excitatory signaling system and an inhibitory signaling system was collapsed by neurosteroid content in the brain varying under stress condition, the various stress-related diseases could be caused by changes of activities in nerve system, immune system and endocrine system which were regulated by these nerve systems. Further, considering it has been reported that pregnenolone sulfate reinforced NMDA-induced cell death in cultured hippocampal nerve cells and caused delayed cell death with DNA fragmentation in neural retina cells, it is suggested that there is possibility that pregnenolone sulfate at least partly takes part in the degeneration of hippocampus CA3 field under stress condition.

As mentioned above, the disrupted balance between an excitatory signaling system and an inhibitory signaling system caused by stressor load can be improved to the desirable balanced condition by the increase or the inhibition of neurosteroid production, which is useful for prevention or treatment for stress-related diseases. Therefore, it is expected that the compounds having affinity for MBRs are extremely useful for prevention and/or treatment for these diseases, if they are supplied.

As therapeutic agent for a stress-related disease, it has been known that the compound represented by formula (X)



(wherein, ring A^Y is C5-8 mono-cyclic carbocyclic ring or 5-8 membered mono-cyclic heterocyclic ring having 1-2 nitrogen atom(s), 1-2 oxygen atom(s) and/or a sulfur atom.; X^Y is $-CH_2-$, $-O-$, $-S-$ etc.; L^{1Y} and L^{2Y} are each independently single bond, C1-4 alkylene or C2-4 alkenylene; R^{1Y} and R^{2Y} are each independently C1-8 alkyl etc.; mY and nY is 0 or an integer of 1-4; R^{3Y} is a hydrogen atom, ring B^Y etc.; ring B^Y is C3-10 mono-cyclic or bi-cyclic carbocyclic ring or mono-cyclic or bi-cyclic heterocyclic ring having 1-2 nitrogen atom(s), 1-2 oxygen atom(s) and/or a sulfur atom; R^{4Y} is a hydrogen atom, C1-8 alkyl etc.), or a pharmaceutically acceptable salt thereof acted to MBRs (see WO03/068753).

In addition, N-phenyl-N'-(2-phenyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)urea (CAS No. 439931-08-5) is known as a reagent.

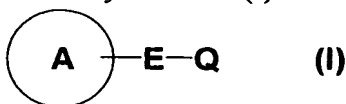
Disclosure of the invention

The problem of the present invention is that the compounds having the affinity to MBRs as a preventive and/or therapeutic agent for a disease caused by a stress are developed.

As a result of the present inventors made further investigation to find out the compound having the affinity to MBRs, they found out that the compounds of the present invention represented by formula (I) accomplished the problems and completed the present invention.

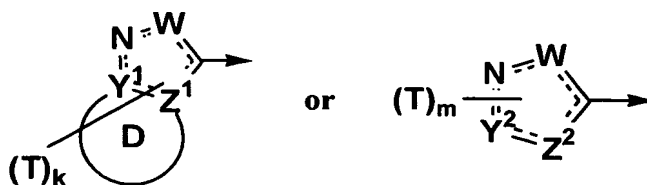
That is, the present invention relates to

[1] A compound represented by formula (I)



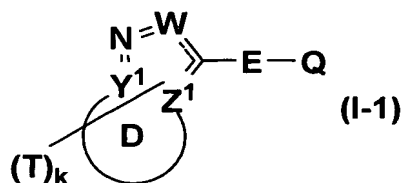
(wherein, ring A is a nitrogen-containing ring which may have a substituent(s), E is a binding bond or a spacer of which main chain has an atom number of 1-8, Q is a hydrocarbon group which may have a substituent(s) or a cyclic group which may have a substituent(s).), a salt thereof, an N-oxide thereof, a solvate thereof, or a prodrug thereof,

[2] The compound according to the above described [1], wherein ring A is



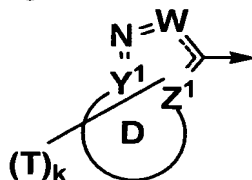
(wherein, W, Y² and Z² are each independently a carbon atom, a nitrogen atom, an oxygen atom or a sulfur atom which may be oxidized, Y¹ and Z¹ are each independently a carbon atom or a nitrogen atom, T is a substituent(s), the symbol represented by ----- is a single bond or a double bond, ring D is C3-8 carbocyclic ring or 3-8 membered heterocyclic ring, k and m are each independently 0 or an integer of 1-5, an arrow is binding to E. However, ring A is not arene structure.),

[3] The compound according to the above described [2], which is represented by formula (I-1)

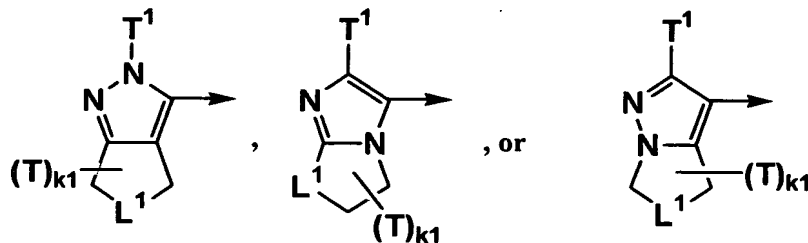


(wherein, all symbols have the same meanings as the above described [1] and [2].),

[4] The compound according to the above described [3], wherein

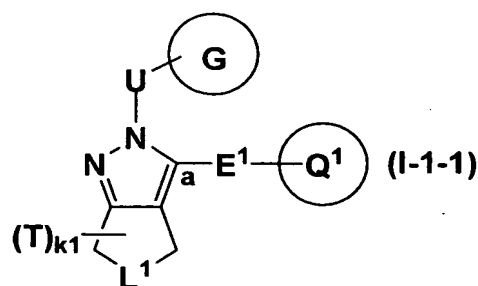


is

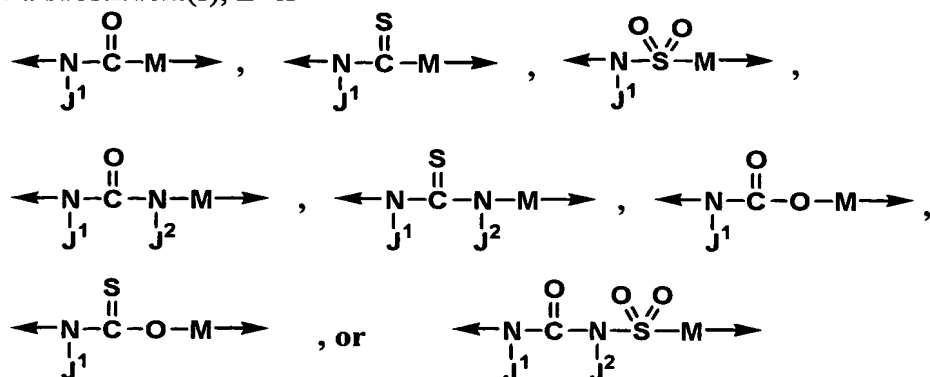


(wherein, L¹ is a binding bond, a nitrogen atom, an oxygen atom, a sulfur atom which may be oxidized or C1-4 alkylene, T¹ is a hydrogen atom(s) or a substituent(s), K1 is 0 or an integer of 1-4, the other symbols have the same meanings as the above described [2]),

[5] The compound according to the above described [3], which is the compound represented by formula (I-1-1)

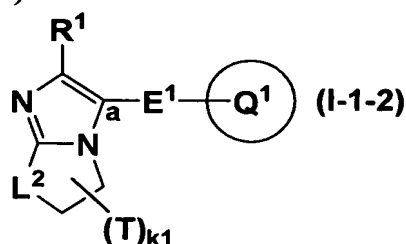


(wherein, U is a binding bond, C1-4 alkylene, C2-4 alkenylene or C2-4 alkynylene, ring G is a carbocyclic ring which may have a substituent(s) or a heterocyclic ring which may have a substituent(s), E¹ is



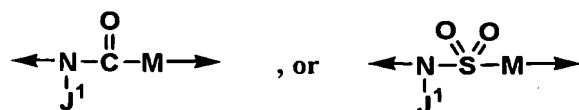
(wherein, a left-pointing arrow is binding to a-position, a right-pointing arrow is binding to ring Q¹, J¹ and J² are each independently a hydrogen atom or a substituent, M is a binding bond or C1-4 alkylene, C2-4 alkenylene or C2-4 alkynylene.), ring Q¹ is a cyclic group which may have a substituent(s), the other symbols have the same meanings as the above described [2] and [4].),

[6] The compound according to the above described [3], which is the compound represented by formula (I-1-2)



(wherein, R¹ is a hydrocarbon group which may have a substituent(s) or a cyclic group which may have a substituent(s), L² is a binding bond, a nitrogen atom or C1-4 alkylene, the other symbols have the same meanings as the above described [2], [4] and [5]. However, N-phenyl-N'-(2-phenyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)urea is excepted.),

[7] The compound according to the above described [5] or [6], wherein E¹ is



(wherein, all symbols have the same meanings as the above described [5]),

[8] The compound according to the above described [5] or [6], wherein L¹ is a nitrogen atom, a sulfur atom which may be oxidized, or C1-4 alkylene,

5 [9] The compound according to the above described [3], which is

(1) N-[2-(4-chlorophenyl)-4,5,6,7-tetrahydro-2H-indazol-3-yl]-2-(4-fluorophenyl)acetamide,

(2) N-[2-(4-chlorophenyl)-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl]-2-phenylacetamide,

10 (3) N-(2-*tert*-butyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-2-phenylacetamide,

(4) 2-phenyl-N-(2-phenyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)acetamide,

(5) 2-(4-fluorophenyl)-N-(2-phenyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)acetamide,

15 (6) N-[2-(4-chlorophenyl)-5-methyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-yl]-2-(4-fluorophenyl)acetamide, or

(7) *tert*-butyl 2-(4-chlorophenyl)-3-[[[(4-fluorophenyl)acetyl]amino]-2,6-dihydropyrrolo[3,4-c]pyrazol-5(4H)-carboxylate,

20 [10] A pharmaceutical composition comprising a compound represented by formula (I) according to the above described [1], a salt thereof, an N-oxide thereof, a solvate thereof or a prodrug thereof,

[11] The pharmaceutical composition according to the above described [10], which is a preventive and/or therapeutic agent for mitochondrial benzodiazepine receptor mediated disease,

25 [12] The pharmaceutical composition according to the above described [11], wherein a mitochondrial benzodiazepine receptor mediated disease is a disease caused by stress,

[13] The pharmaceutical composition according to the above described [12], wherein a disease caused by stress is a central nervous system disease caused by stress, a respiratory system disease caused by stress and/or digestive system disease caused by stress,

30 [14] The pharmaceutical composition according to the above described [13], wherein a central nervous system caused by stress is anxiety-related disease, sleep

disorder, depression and/or epilepsy, a respiratory system disease caused by stress is asthma, a digestive system disease caused by stress is irritable bowel syndrome,

[15] A pharmaceutical composition combining of the compound represented by formula (I) according to the above described [1], a salt thereof, an N-oxide thereof, a solvate thereof or a prodrug thereof and one kind or more kind selected from antianxiety drugs, antidepressant drugs, antiparkinson drugs, therapeutic drugs for schizophrenia, antiepileptic drugs, therapeutic drugs for asthma, therapeutic drugs for peptic ulcer, adjustive drugs for gastrointestinal function, antidiarrheals, evacuants, antihypertensive drugs, antiarrhythmic drugs, inotropic drugs and therapeutic drugs for urination disorder,

[16] A method for prevention and/or treatment for a mitochondrial benzodiazepine receptor mediated disease in mammals is characterized by administration effective dose of the compound represented by formula (I) according to the above described [1], a salt thereof, an N-oxide, a solvate or a prodrug thereof to the mammals, and

[17] The use of the compound represented by formula (I) according to the above described [1], a salt thereof, an N-oxide thereof, a solvate thereof or a prodrug thereof for preparing a preventive and/or therapeutic agent for a mitochondrial benzodiazepine receptor mediated disease.

In the specification, a disease caused by stress includes, for example, central nervous system disease caused by stress, respiratory system disease caused by stress, digestive system disease caused by stress, cardiovascular system disease caused by stress, uropathy/reproductive system disease caused by stress, gynecologic disease caused by stress, endocrine/metabolic disease caused by stress, ophthalmologic disease caused by stress, otolaryngological disease caused by stress, dental surgery /dentistry disease caused by stress, surgical/orthopedic disease caused by stress, skin disease caused by stress, other disease caused by stress. Central nervous system disease caused by stress, respiratory system disease caused by stress and/or digestive system disease caused by stress is/are preferred.

In the specification, central nervous system disease caused by stress includes, for example, anxiety related disease, neurosis, panic disorder, sleep disorder, depression, reactive depression, epilepsy, Parkinson's disease, Perkinsonian syndrome, schizophrenia, autonomic imbalance, Huntington's disease, Alzheimer's disease, affective disorder, cognitive disorder, migraine, tension headache, cluster headache, posttraumatic stress disorder (PTSD), dissociative disorder, insomnia, nervous vomiting, nervous cough, psychogenic convulsive seizure, psychogenic syncopal attack,

maladjustment to job, burn-out syndrome, chronic fatigue syndrome, writer's cramp, spastic torticollis and so on. Anxiety related disease, sleep disorder, depression and/or epilepsy is/are preferred.

In the specification, respiratory system disease caused by stress includes, for example, asthma, bronchial asthma, hyperventilation syndrome, laryngospasm, chronic obstructive pulmonary disease and so on. Asthma is preferred.

In the specification, digestive system disease caused by stress includes, for example, irritable bowel syndrome, peptic ulcer, functional dyspepsia, gastric ulcer, duodenal ulcer, ulcerative colitis, biliary tract dyskinesia, esophagospasm, gastric atony, aerophagy, chronic hepatitis, chronic pancreatitis and so on. Irritable bowel syndrome is preferred.

In the specification, cardiovascular system disease caused by stress includes, for example, essential hypertension, arrhythmia, (neurological) angina pectoris, essential hypotension, orthostatic dysregulation, myocardial infarction, arteriosclerosis, vertigo and so on. Essential hypertension, arrhythmia and/or angina pectoris is/are preferred.

In the specification, uropathy/reproductive system disease caused by stress includes, for example, dysuria, nervous pollakiuria (irritable bladder), nocturia, enuresis, psychogenic ischuria, impotentia, prostatism, urethral syndrome and so on. Dysuria is preferred.

In the specification, gynecologic disease caused by stress includes, for example, menopausal disorder, menorrhagia, emmeniopathy, premenstrual syndrome, infertility, frigidity, hyperemesis, abortion, premature birth and so on.

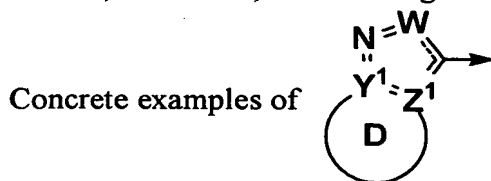
In the specification, endocrine/metabolic disease caused by stress includes, for example, anorexia nervosa, eating disorder, cibophobia, bulimia, Bartter's syndrome, hyperthyroidism, glucose metabolism disorder (*e.g.* diabetes, (reflex) hypoglycemia *etc.*), lipid metabolism disorder (*e.g.* hyperlipemia *etc.*), gout, osteoporosis, hypothalamus disease, pituitary gland disease, accessory thyroid gland disease, adrenal cortex/adrenal medulla disease, gonad disease, psychogenic polydipsia, adiposity and so on.

In the specification, ophthalmologic disease caused by stress includes, for example, asthenopia, central retinitis, muscae volitantes, blepharospasm, primary glaucoma, vertigo and so on.

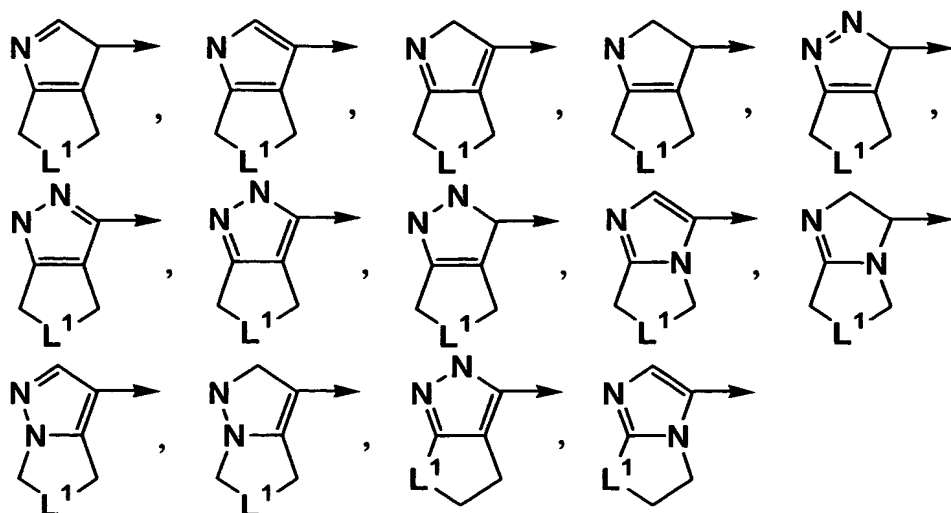
In the specification, otolaryngological diseases caused by stress includes, for example, susurrus aurium, vertigo, psychogenic deafness, chronic sinusitis, allergic rhinitis, smell disorder, stuttering, aphonia and so on.

cycloheptene, cyclooctene, cyclopentadiene, cyclohexadiene, cycloheptadiene, cyclooctadiene, benzene ring *etc.*

“C3-8 heterocyclic ring” represented by ring D means, for example, pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyran, oxepine, thiophene, thiopyran, thiepine, oxazole, isoxazole, thiazole, isothiazole, furazan, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepine, aziridine, azetidine, pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydroazepine, tetrahydroazepine, perhydroazepine, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, oxetane, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrooxepine, tetrahydrooxepine, perhydrooxepine, thietane, dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrothiepine, tetrahydrothiepine, perhydrothiepine, dihydrooxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isoxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydrothiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, dihydrothiazpine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepine, tetrahydrothiadiazepine, perhydrothiadiazepine, morpholine, thiomorpholine, oxathiane, dioxolane, dioxane, dithiolane, dithiane ring *etc.*



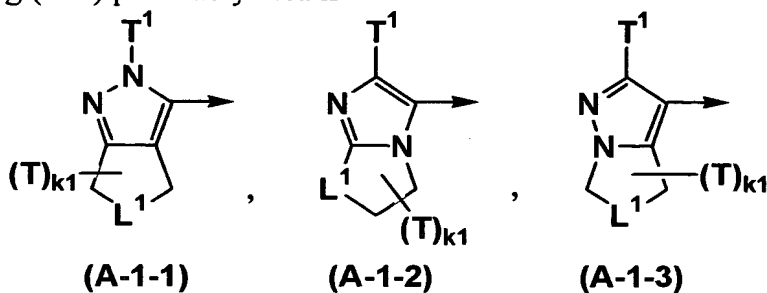
(wherein, all symbols have the same meanings as the described above.) in ring (A-1)
mean



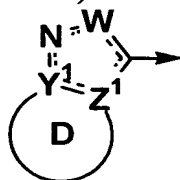
and so on.

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Ring (A-1) preferably means

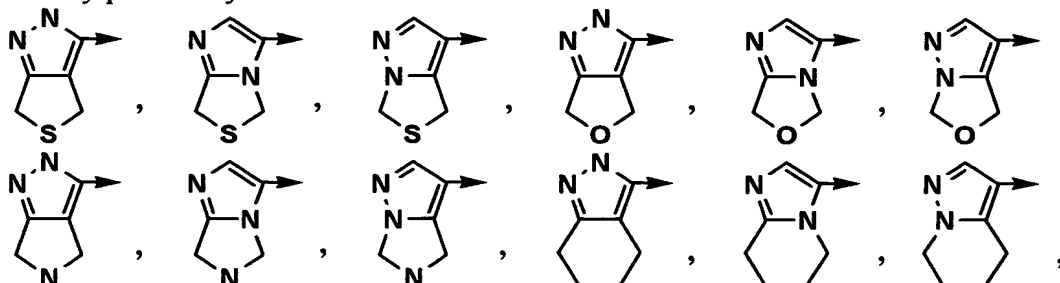


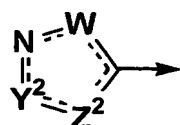
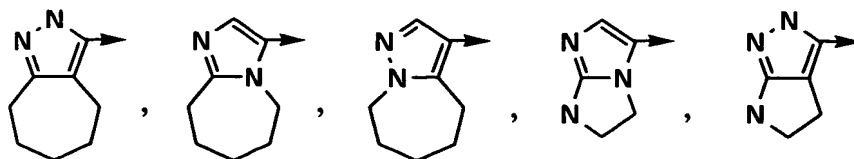
(wherein, all symbols have the same meanings as the described above.) and more preferably means ring (A-1-1), ring (A-1-2).



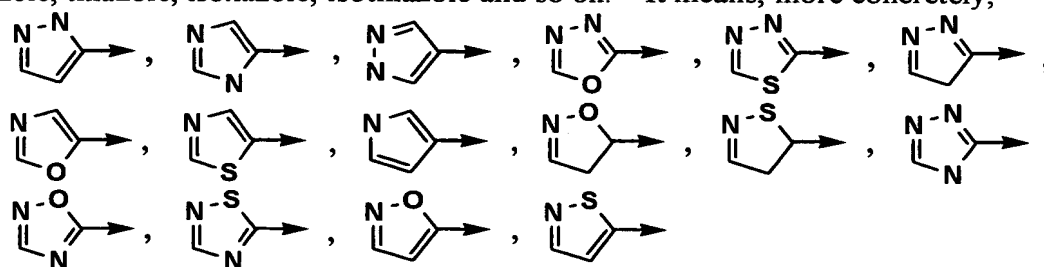
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(wherein, all symbols have the same meanings as the described above.) in ring (A-1) particularly preferably means



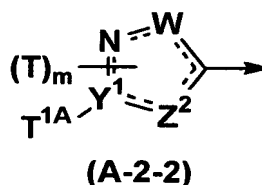
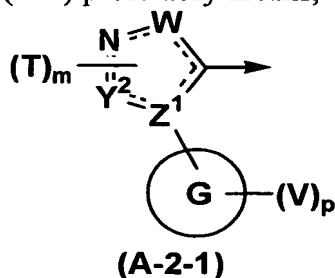


(wherein, all symbols have the same meanings as the described above.) in ring A (A-2) means, for example, pyrazole, imidazole, pyrrole, triazole, oxadiazole, thiadiazole, oxazole, thiazole, isoxazole, isothiazole and so on. It means, more concretely,



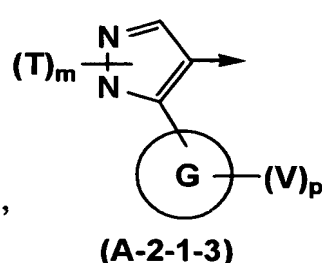
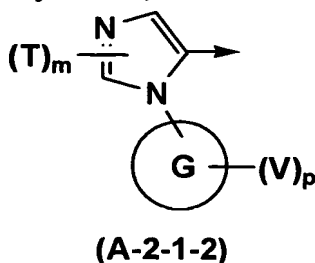
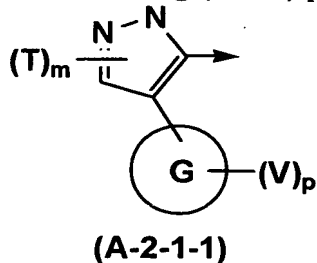
10 and so on.

Ring (A-2) preferably means,



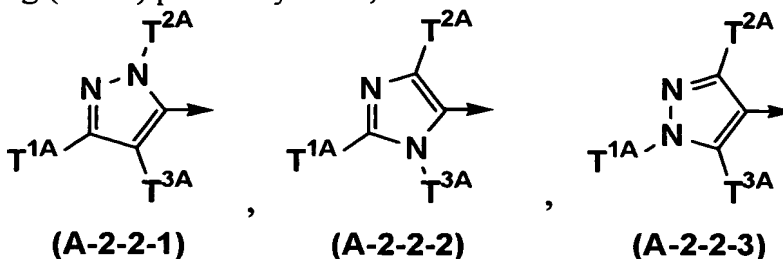
(wherein, ring G is carbocyclic ring which may have a substituent(s) or heterocyclic ring which may have a substituent(s), p is 0 or an integer of 1-5, V is a substituent(s), T^{1A} is straight-chain or branched-chain C1-8 alkyl, the other symbols have the same meanings as the described above.) and so on.

Ring (A-2-1) preferably means,



(wherein, all symbols have the same meanings as the described above.).

Ring (A-2-2) preferably mean,



(wherein, T^{2A} and T^{3A} are each independently hydrogen atom or substituent, the other symbols have the same meanings as the described above.).

5 In the specification, "substituent" in "nitrogen-containing ring which may have a substituent(s)" represented by ring A means, for example, (1) alkyl which may have a substituent(s), (2) alkenyl which may have a substituent(s), (3) alkynyl which may have a substituent(s), (4) carbocyclic ring which may have a substituent(s), (5) heterocyclic ring which may have a substituent(s), (6) hydroxyl which may have a substituent(s), (7) mercapto which may have a substituent(s), (8) amino which may have a substituent(s), (9) carbamoyl which may have a substituent(s), (10) sulfamoyl which may have a substituent(s), (11) carboxyl, (12) (alkyl which may have a substituent(s)) oxycarbonyl, (13) sulfo, (14) sulfinio, (15) phosphono, (16) nitro, (17) cyano, (18) amidino, (19) imino, (20) dihydroxyboryl, (21) halogen atom (fluorine, chlorine ,
 10 bromine , iodine), (22) alkylsulfinyl (*e.g.* C1-4 alkylsulfinyl *etc.*, such as methylsulfinyl, ethylsulfinyl and so on), (23) heterocyclic ring sulfinyl (*e.g.* C6-10 aromatic ring sulfinyl *etc.*, such as phenylsulfinyl and so on), (24) alkylsulfonyl (*e.g.* C1-4 alkylsulfonyl *etc.*, such as methylsulfonyl, ethylsulfonyl and so on), (25) heterocyclic ring sulfonyl (*e.g.* C6-10 heterocyclic ring sulfonyl *etc.*, such as phenylsulfonyl and so on), (26) acyl, (27) oxo, (28) thioxo, (29) (C1-6 alkoxyimino)methyl (*e.g.* (methoxyimino)methyl *etc.*) and so on. These optional substituents may be substituted
 15 1-5 at the replaceable position.

In addition, in case of the substituents are plural, two substituents may be together with one or two their binding carbon atom to form C3-10 mono-aromatic
 25 carbocyclic ring, the carbocyclic ring partially or fully saturated, or 3-10 membered mono-aromatic heterocyclic ring cotaining 1-2 hetero atom(s) selected from an oxygen atom(s), a nitrogen atom(s) and a sulfur atom(s) partially or fully saturated and so on. C3-10 mono-aromatic carbocyclic ring, the carbocyclic ring partially or fully saturated means, for example, cyclopropane, cyclobutane, cyclopentane, cyclohexane,
 30 cycloheptane, cyclooctane, cyclononane, cyclodecane, cyclopentene, cyclohexene, cycloheptene, cylooctene, cyclopentadiene, cyclohexadiene, cycloheptadiene, cyclooctadiene and so on. 3-10 membered mono-aromatic heterocyclic ring cotaining

1-2 hetero atom(s) selected from an oxygen atom(s), a nitrogen atom(s) and/or a sulfur atom(s) partially or fully saturated means, for example, aziridine, azetidine, pyrroline, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydroazepine, tetrahydroazepine, perhydroazepine, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, oxirane, oxetane, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrooxepine, tetrahydrooxepine, perhydrooxepine, thiirane, thietane, dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrothiepine, tetrahydrothiepine, perhydrothiepine, dihydrooxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isoxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrothiazine, tetrahydrothiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, morpholine, thiomorpholine, oxathiane, dioxolane, dioxane, dithiolane, dithiane ring and so on.

Alkyl in "(1) alkyl which may have a substituent(s)" as substituent means, for example, straight-chain or branched-chain C1-20 alkyl *etc.*, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icocyl and so on. Here, the substituent of alkyl means, for example, hydroxyl, mercapto, amino, carboxyl, nitro, cyano, mono-, or di-C1-6 alkylamino (*e.g.* methylamino, ethylamino, propylamino, dimethylamino, diethylamino *etc.*), N-heterocyclic ring amino (*e.g.* N-phenylamino *etc.*), N-heterocyclic ring-N-alkylamino (*e.g.* N-phenyl-N-methylamino, N-phenyl-N-ethylamino, N-phenyl-N-propylamino, N-phenyl-N-butylamino, N-phenyl-N-pentylamino, N-phenyl-N-hexylamino *etc.*), acylamino, N-acyl-N-alkylamino, C1-6 alkoxy (*e.g.* methoxy, ethoxy, propoxy, isopropoxy, hexyloxy *etc.*), C3-7 cycloalkyl-C1-6 alkoxy (*e.g.* cyclohexylmethyloxy, cyclopentylethyloxy *etc.*), C3-7 cycloalkyloxy (*e.g.* cyclohexyloxy *etc.*), C7-15 aralkyloxy (*e.g.* benzyloxy, phenethyloxy, phenylpropyloxy, naphthylmethyloxy, naphthylethyloxy *etc.*), phenoxy, C1-6 alkoxycarbonyl (*e.g.* methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl *etc.*), C1-6 alkylcarbonyloxy (*e.g.* acetoxyl, ethylcarbonyloxy *etc.*), C1-6 alkylthio (*e.g.* methylthio, ethylthio, propylthio, isopropylthio, butylthio, pentylthio, hexylthio *etc.*), halogen atom (fluorine, chlorine, bromine, iodine), alkylsulfonyl (*e.g.* C1-4 alkyl sulfonyl *etc.*, such as

methysulfonyl, ethylsulfonyl and so on.), heterocyclic sulfonyl (*e.g.* C6-10 heterocyclic ring sulfonyl *etc.*, such as phenylsulfonyl and so on.), carbamoyl which may have a substituent(s) (*e.g.* unsubstituted carbamoyl, N-mono-C1-6 alkylcarbamoyl (*e.g.* N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-isopropylcarbamoyl, N-butylcarbamoyl *etc.*), N,N-di-C1-6 alkylcarbamoyl (*e.g.* N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N,N-dipropylcarbamoyl, N,N-dibutylcarbamoyl *etc.*), piperidine-1-ylcarbonyl *etc.*), acyl, carbocyclic ring which may have a substituent(s), heterocyclic ring which may have a substituent(s) and so on. These optional substituents may be substituted 1-5 at the replaceable position. Here, alkyl in N-acyl-N-alkylamino means, for example, straight-chain or branched chain C1-6 alkyl *etc.*, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, hexyl and so on. In addition, acyl in acyl, acylamino and N-acyl-N-alkylamino has the same meanings as the below described “(26) acyl”. Additionally, carbocyclic ring which may have a substituent(s) and heterocyclic which may have a substituent(s) have the same meanings as the below described “(4) carbocyclic ring which may have a substituent(s)” and “(5) heterocyclic ring which may have a substituent(s)”.

Alkenyl in “(2) alkenyl which may have a substituent(s)” as substituent means, for example, straight-chain or branched-chain C2-8 alkenyl *etc.*, such as ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl and so on. Here the substituent of alkenyl has the same meanings as the above described “(1) alkyl which may have a substituent(s)”.

Alkynyl in “(3) alkynyl which may have a substituent(s)” as substituent means, for example, straight-chain or branched-chain C2-8 alkynyl *etc.*, such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl and so on. Here the substituent of alkynyl has the same meanings as the above described “(1) alkyl which may have a substituent(s)”.

Carbocyclic ring “(4) carbocyclic ring which may have a substituent(s)” as substituent means, for example, C3-20 mono-, bi-, tri- or tetra-carbocyclic ring and so on. Concretely, it means C3-20 mono-, bi-, tri- or tetra-aromatic carbocyclic ring partially or fully saturated, spiro-linked bi-, tri-, or tetra-carbocyclic ring, and bridged bi-, tri-, or tetra-carbocyclic ring and so on. C3-20 mono-, bi-, tri- or tetra-aromatic carbocyclic ring partially or fully saturated means, for example, benzene, azulene, naphthalene, phenanthrene, anthracene, triphenylene, chrysene, naphthacene, pleiadene, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cycloundecane, cyclododecane, cyclotridecane, cyclotetradecane, cyclopentadecane, cyclopentene, cyclohexene, cycloheptene,

cyclooctene, cyclopentadiene, cyclohexadiene, cycloheptadiene, cyclooctadiene, pentalene, perhydropentalene, perhydroazulene, indene, perhydroindene, indane, dihydronaphthalene, tetrahydronaphthalene, perhydronaphthalene, heptalene, perhydroheptalene, biphenylene, as-indacene, s-indacene, acenaphthylene, acenaphthene, fluorene, phenalene, fluoranthene, acephenanthrylene, aceanthrylene, pyrene and so on. Spiro-linked bi-, tri-, or tetra-carbocyclic ring, and bridged bi-, tri-, or tetra-carbocyclic ring mean, for example, spiro[4.4]nonane, spiro[4.5]decane, spiro[5.5]undecane, bicyclo[2.2.1]heptane, bicyclo[2.2.1]hepta-2-ene, bicyclo[3.1.1]heptane, bicyclo[3.1.1]hepta-2-ene, bicyclo[2.2.2]octane, bicyclo[2.2.2]octa-2-ene, adamantane, noradamantane and so on.

Substituent in “(4) carbocyclic ring which may have a substituent(s)” means, for example, straight-chain or branched-chain C1-8 alkyl (*e.g.* methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, hexyl, heptyl, octyl *etc.*) which may be substituted with hydroxyl, straight-chain or branched-chain C2-6 alkenyl (*e.g.* ethenyl, propenyl, butenyl, pentenyl, hexenyl *etc.*), straight-chain or branched-chain C2-6 alkynyl (*e.g.* ethynyl, propynyl, butynyl, pentynyl, hexynyl *etc.*), hydroxyl, straight-chain or branched-chain C1-6 alkoxy (*e.g.* methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutyloxy, *tert*-butoxy, pentyloxy, hexyloxy *etc.*), mercapto, straight-chain or branched-chain C1-6 alkylthio (*e.g.* methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, *tert*-butylthio, pentylthio, hexylthio *etc.*), amino, mono- or di-C1-6 alkylamino (*e.g.* methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, *tert*-butylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, N-methyl-N-ethylamino *etc.*), halogen atom (fluorine, chlorine, bromine, iodine), cyano, nitro, carboxyl, straight-chain or branched-chain C1-6 alkoxycarbonyl (*e.g.* methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl *etc.*), straight-chain or branched-chain C1-6 alkylcarbonyloxy (*e.g.* acetoxyl, ethylcarbonyloxy *etc.*), trihalomethyl (*e.g.* trifluoromethyl *etc.*), trihalomethoxy (*e.g.* trifluoromethoxy *etc.*), trihalomethylthio (*e.g.* trifluoromethylthio *etc.*), dihalomethylthio (*e.g.* difluoromethylthio *etc.*), oxo, carbocyclic ring (it has the same meanings as the above described “(4) carbocyclic ring which may have a substituent(s)”), heterocyclic ring (it has the same meanings as the above described “(5) heterocyclic ring which may have a substituent(s)”) and so on. These optional substituents may be substituted 1-4 at the replaceable position.

Heterocyclic ring in “(5) heterocyclic ring which may have a substituent(s)” as substituent means, for example, 3-20 membered mono-, bi-, tri-, or tetra heterocyclic ring containing 1 to 5 hetero atom(s) selected from oxygen atom(s), nitrogen atom(s)

and/or sulfur atom(s) and so on. Concretely, it means 3-20 membered mono-, bi-, tri-, or tetra-aromatic heterocyclic ring optionally partially or fully saturated containing 1 to 5 hetero atom(s) selected from oxygen atom(s), nitrogen atom(s) and/or sulfur atom(s) and so on. 3-20 membered mono-, bi-, tri-, or tetra-aromatic heterocyclic ring optionally partially or fully saturated containing 1 to 5 hetero atom(s) selected from oxygen atom(s), nitrogen atom(s) and/or sulfur atom(s) means, for example, pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyran, oxepine, thiophene, thiopyran, thiepine, oxazole, isoxazole, thiazole, isothiazole, furazan, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepine, indole, isoindole, indolizine, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, dithianaphthalene, indazole, quinoline, isoquinoline, quinolizine, purine, phthalazine, pteridine, naphthyridine, quinoxaline, quinazoline, cinnoline, pyrrolopyridine, benzoxazole, benzothiazole, benzimidazole, chromene, benzoxepine, benzoxazepine, benzoxadiazepine, benzothiepine, benzothiazepine, benzothiadiazepine, benzazepine, benzodiazepine, benzofurazan, benzothiadiazole, benzotriazole, carbazole, beta-carboline, acridine, phenazine, dibenzofuran, xanthene, dibenzothiophene, phenothiazine, phenoxazine, phenoxathiin, thianthrene, phenanthridine, phenanthroline, perimidine, pyridonaphthyridine, pyrazoloisoquinoline, pyrazolonaphthyridine, pyrimidoindole, indolizinoindole, aziridine, azetidine, pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydroazepine, tetrahydroazepine, perhydroazepine, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, oxirane, oxetane, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrooxepine, tetrahydrooxepine, perhydrooxepine, thiirane, thietane, dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrothiepine, tetrahydrothiepine, perhydrothiepine, dihydrooxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isoxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine),

dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine,
 dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepine,
 tetrahydrothiadiazepine, perhydrothiadiazepine, morpholine, thiomorpholine, oxathiane,
 indoline, isoindoline, dihydrobenzofuran, perhydrobenzofuran, dihydroisobenzofuran,
 5 perhydroisobenzofuran, dihydrobenzothiophene, perhydrobenzothiophene,
 dihydroisobenzothiophene, perhydroisobenzothiophene, dihydroindazole,
 perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline,
 dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine,
 tetrahydrophthalazine, perhydrophthalazine, dihydronaphththyridine,
 10 tetrahydronaphththyridine, perhydronaphththyridine, dihydroquinoxaline,
 tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline, tetrahydroquinazoline,
 perhydroquinazoline, tetrahydropyrrolopyridine, dihydrocinnoline, tetrahydrocinnoline,
 perhydrocinnoline, benzoxathiane, dihydrobenzoxazine, dihydrobenzothiazine,
 pyrazinomorpholine, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole,
 15 perhydrobenzothiazole, dihydrobenzimidazole, perhydrobenzimidazole,
 dihydrobenzazepine, tetrahydrobenzazepine, dihydrobenzodiazepine,
 tetrahydrobenzodiazepine, benzodioxepane, dihydrobenzoxazepine,
 tetrahydrobenzoxazepine, dihydrocarbazole, tetrahydrocarbazole, perhydrocarbazole,
 dihydroacridine, tetrahydroacridine, perhydroacridine, dihydrodibenzofuran,
 20 dihydrodibenzothiophene, tetrahydrodibenzofuran, tetrahydrodibenzothiophene,
 perhydrodibenzofuran, perhydrodibenzothiophene, tetrahyridonaphththyridine,
 tetrahydro-beta-carboline, dihydroazepinoindole, hexahydroazepinoindole,
 tetrahydropyrazoloisoquinoline, tetrahydropyrazolonaphththyridine,
 dihydroazepinoindazole, hexahydroazepinoindazole, dihydropyrazolopyridoazepine,
 25 hexahydropyrazolopyridoazepine, tetrahydropyrimidoindole, dihydrothiazinoindole,
 tetrahydrothiazinoindole, dihydrooxazinoindole, tetrahydrooxazinoindole,
 hexahydroindolizinoindole, dihydroindolobenzdiazepine, octahydroindoloquinolizine,
 hexahydroimidazopyridoindole, hexahydropyrrolothiazepinoindole, dioxolane, dioxane,
 dithiolane, dithiane, dioxaindan, benzodioxane, chroman, benzodithiolane,
 30 benzodithiane, azaspiro[4.4]nonane, oxazaspiro[4.4]nonane, oxazaspiro[2.5]octane,
 dioxaspiro[4.4]nonane, azaspiro[4.5]decane, thiaspiro[4.5]decane,
 dithiaspiro[4.5]decane, dioxaspiro[4.5]decane, oxazaspiro[4.5]decane,
 azaspiro[5.5]undecane, oxaspiro[5.5]undecane, dioxaspiro[5.5]undecane, 2,3,4,9-
 tetrahydrospiro[beta-carboline-1,1'-cyclopentane], azabicyclo[2.2.1]heptane,
 35 oxabicyclo[2.2.1]heptane, azabicyclo[3.1.1]heptane, azabicyclo[3.2.1]octane,
 oxabicyclo[3.2.1]octane, azabicyclo[2.2.2]octane, diazabicyclo[2.2.2]octane and so on.

Substituent in “(5) heterocyclic ring which may have a substituent(s)” has the same meanings as the above described substituent in “(4) carbocyclic ring which may have a substituent(s)”. These optional substituents may be substituted 1-4 at the replaceable position.

5 Substituent in “(6) hydroxyl which may have a substituent(s)”, “(7) mercapto which may have a substituent(s)” and “(8) amino which may have a substituent(s)” as substituent means, for example, alkyl which may have a substituent(s) (it has the same meanings as the above described “(1) alkyl which may have a substituent(s)”), alkenyl which may have a substituent(s) (it has the same meanings as
10 the above described “(2) alkenyl which may have a substituent(s)”), alkynyl which may have a substituent(s) (it has the same meanings as the above described “(3) alkynyl which may have a substituent(s)”), carbocyclic ring which may have a substituent(s) (it has the same meanings as the above described “(4) carbocyclic ring which may have a substituent(s)”), heterocyclic ring which may have a substituent(s) (it has the same
15 meanings as the above described “(5) heterocyclic ring which may have a substituent(s)”), alkylsulfonyl (*e.g.* C1-4 alkylsulfonyl *etc.*, such as methylsulfonyl, ethylsulfonyl and so on.), heterocyclic sulfonyl (*e.g.* C6-10 heterocyclic ring sulfonyl *etc.*, such as phenylsulfonyl and so on.), acyl (it has the same meanings as the below described “(26) acyl”) and so on. In addition, in case of “(8) amino which may have a
20 substituent(s)”, these optional substituents may be substituted 1-2 at the replaceable position.

Substituent in “(9) carbamoyl which may have a substituent(s)” and “(10) sulfamoyl which may have a substituent(s)” as substituent means, for example, alkyl which may have a substituent(s) (it has the same meanings as the above described “(1)
25 alkyl which may have a substituent(s)”), alkenyl which may have a substituent(s) (it has the same meanings as the above described “(2) alkenyl which may have a substituent(s)”), alkynyl which may have a substituent(s) (it has the same meanings as the above described “(3) alkynyl which may have a substituent(s)”), carbocyclic ring which may have a substituent(s) (it has the same meanings as the above described “(4)
30 carbocyclic ring which may have a substituent(s)”), heterocyclic ring which may have a substituent(s) (it has the same meanings as the above described “(5) heterocyclic ring which may have a substituent(s)”) and so on. These optional substituents may be substituted 1-2 at the replaceable position.

Alkyl which may have a substituent(s) in “(12) (alkyl which may have a
35 substituent(s)) oxycarbonyl” as substituent has the same meanings as the above described “(1) alkyl which may have a substituent(s)”.

“(26) acyl” as substituent means, for example, formyl, alkylcarbonyl which may have a substituent(s) (wherein, alkyl which may have a substituent(s) has the same meanings as the above described “(1) alkyl which may have a substituent(s)”, alkenylcarbonyl which may have a substituent(s) (wherein, alkenyl which may have a substituent(s) has the same meanings as the above described “(2) alkenyl which may have a substituent(s)”), alkynylcarbonyl which may have a substituent(s) (wherein, alkynyl which may have a substituent(s) has the same meanings as the above described “(3) alkynyl which may have a substituent(s)”), carbocyclic ring carbonyl which may have a substituent(s) (wherein, carbocyclic ring which may have a substituent(s) has the same meanings as the above described “(4) carbocyclic ring which may have a substituent(s)”), heterocyclic ring carbonyl which may have a substituent(s) has the same meanings as the above described “(5) heterocyclic ring which may have a substituent(s)” and so on.

“Substituent” represented by T, T¹, T², T³, T^{2A}, T^{3A} or V has the same meanings as the above described substituent in “nitrogen-containing heterocyclic ring which may have a substituent(s)” represented by ring A.

In the specification, “binding bond” represented by E means ring A and substituent Q directly binding without intervention of other atoms.

In the specification, “a spacer of which main chain has an atom number of 1-8” represented by E means the distance that 1-8 atom(s) of main chain is(are) connected. Here, “atom number of main chain” is counted to be minimal. “A spacer of which main chain has an atom number of 1-8” means, for example, divalent group combining voluntarily 1-8 selected from methylene (-CH₂-) which may have 1 or 2 substituent(s), ethenylene (-CH=CH-) which may have 1 or 2 substituent(s), ethynylene (-CH≡CH-), nitrogen atom (-NH-) which may have a substituent, -CO-, -O-, -S-, -SO- and -SO₂- and so on. Concretely, it means -CR¹⁰¹R¹⁰²-, -CR¹⁰¹=CR¹⁰²-, -C≡C-, -NR¹⁰³-, -CO-, -O-, -S-, -NJ¹CO-, CONJ¹-, NJ¹CONJ²-, -NJ¹SO₂-, -SO₂NJ¹-, -NR¹⁰³COCR¹⁰¹R¹⁰²- and -CONR¹⁰³CR¹⁰¹R¹⁰²- (wherein, R¹⁰¹, R¹⁰², R¹⁰³, J¹ and J² are each independently hydrogen atom, or have the same meanings as the above described substituent in “nitrogen-containing heterocyclic ring” represented by ring A) and so on.

In the specification, “hydrocarbon group which may have a substituent(s)” represented by Q or R¹ has the same meanings as “(1) alkyl which may have a substituent(s)”, “(2) alkenyl which may have a substituent” or “(3) alkynyl which may have a substituent” in “substituent” of “nitrogen-containing heterocyclic ring” represented by the above described ring A.

In the specification, "cyclic group" in "cyclic group which may have a substituent(s)" represented by Q or ring Q¹ means, for example, carbocyclic ring (it has the same meanings as the above described carbocyclic ring in "(4) carbocyclic ring which may have a substituent(s)" in substituent of "nitrogen-containing heterocyclic ring which may have a substituent(s)" represented by ring A), heterocyclic ring (it has the same meanings as the above described heterocyclic ring in "(5) heterocyclic ring which may have a substituent(s)" in substituent of "nitrogen-containing heterocyclic ring which may have a substituent(s)" represented by ring A) and so on.

"Substituent" in "cyclic group which may have a substituent(s)" represented by Q, R¹ or ring Q¹ has the same meanings as the "substituent" in "nitrogen-containing heterocyclic ring which may have a substituent(s)" represented by the above described ring A. These optional substituents may be substituted 1-5 at the replaceable position.

In the specification, "carbocyclic ring which may have a substituent(s)" represented by ring G has the same meanings as "(4) carbocyclic ring which may have a substituent(s)" in the substituent of "nitrogen-containing heterocyclic ring which may have a substituent(s)" represented by the above described ring A.

In the specification, "heterocyclic ring which may have a substituent(s)" represented by ring G has the same meanings as "(5) heterocyclic ring which may have a substituent(s)" in the substituent of "nitrogen-containing heterocyclic ring which may have a substituent(s)" represented by the above described ring A.

In the specification, "C1-4 alkylene" represented by L¹ or L² means, for example, methylene, ethylene, propylene, butylene and so on.

In the specification, "a sulfur atom which may be oxidized" represented by W, Y², Z² or L¹ means -S-, -S(O)- or -SO₂-.

In the specification, "C1-4 alkylene" represented by M or U means, for example, straight-chain or branched-chain C1-4 alkylene *etc.*, such as methylene, ethylene, propylene, butylene and so on.

In the specification, "C2-4 alkenylene" represented by M or U means, for example, straight-chain or branched-chain C2-4 alkenylene *etc.*, such as ethenylene, propenylene, butenylene and so on.

In the specification, "C2-4 alkynylene" represented by M or U means, for example, straight-chain or branched-chain C2-4 alkynylene *etc.*, such as ethynylene, propynylene, butynylene and so on.

"Substituent" in "nitrogen-containing ring which may have a substituent(s)" represented by ring A, or "cyclic group which may have a substituent(s)" or "hydrocarbon group which may have a substituent(s)" represented by Q preferably

means 1-5 substituent(s) voluntary selected from C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, C1-8 alkoxy or C1-8 alkylthio which may be substituted with 1-5 $R^2(s)$ (wherein, C1-8 alkoxy means, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, *tert*-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy and so on, C1-8 alkylthio means, for example, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, *tert*-butylthio, pentylthio, hexylthio, heptylthio, octylthio and so on, R^2 means, for example, hydroxyl, halogen atom or phenyl and so on.), carbocyclic ring (*e.g.* benzene, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, naphthalene, indane *etc.*) which may be substituted with 1-3 $R^3(s)$ (wherein, R^3 means C1-4 alkyl, halogen atom, nitro, cyano, C1-4 alkoxy, C1-4 alkoxycarbonyl and so on.) or heterocyclic ring (*e.g.* pyridine, pyrazine, pyrrole, pyrimidine, piperazine, pyrrolidine, thiophene, furan, tetrahydrothiophene, tetrahydrofuran, pyran, dioxane *etc.*), -O-(carbocyclic ring which may be substituted with 1-3 $R^3(s)$), -O-(heterocyclic ring which may be substituted with 1-3 $R^3(s)$), hydroxyl, mercapto, amino, NR^4R^5 (wherein, R^4 and R^5 are each independently hydrogen atom or C1-8 alkyl), carboxyl, C1-8 alkoxycarbonyl, nitro, cyano, halogen atom, C1-6 acyl (*e.g.* formyl, ethanoyl, propanoyl, butanoyl, pentanoyl, hexanoyl *etc.*), oxo and oxo. It more preferably means 1-3 substituent(s) voluntary selected from C1-4 alkyl (*e.g.* methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, sec-butyl *etc.*), C1-4 alkoxycarbonyl (*e.g.* methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl *etc.*), C1-4 alkoxycarbonyl (*e.g.* methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl *etc.*), methoxy, isopropoxy, trifluoromethyl, trifluoromethoxy, difluoromethoxy, halogen atom, cyano, pyridinyl, oxo, phenoxy, phenyl which may be substituted with 1-3 $R^3(s)$ and cyclohexyl. It further preferably means methyl, *tert*-butyl, phenyl which may be substituted with 1-3 $R^3(s)$, *tert*-butoxycarbonyl and benzyl.

“Substituent” represented by T, T^1 , T^2 , T^3 or V preferably means C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, C1-8 alkoxy, or C1-8 alkylthio which may be substituted with 1-5 $R^2(s)$ (wherein, C1-8 alkoxy means, for example methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, *tert*-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy and so on, C1-8 alkylthio means, for example, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, *tert*-butylthio, pentylthio, hexylthio, heptylthio, octylthio and so on, R^2 means, for example, hydroxyl, halogen atom, phenyl and so on.), carbocyclic ring (*e.g.* benzene, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, naphthalene, indane *etc.*) which may be substituted with 1-3 $R^3(s)$ (wherein, R^3 is C1-4 alkyl, halogen atom, nitro, cyano, C1-4 alkoxy, C1-4 alkoxycarbonyl and so on.) or heterocyclic ring (*e.g.* pyridine,

pyrazine, pyrrole, pyrimidine, piperazine, pyrrolidine, thiophene, furan, tetrahydrothiophene, tetrahydrofuran, pyran, dioxane *etc.*), -O-(carbocyclic ring which may be substituted with 1-3 R³(s)), -O-(heterocyclic ring which may be substituted with 1-3 R³(s)), mercapto, amino, NR⁴R⁵ (wherein, R⁴ and R⁵ are each independently hydrogen atom or C1-8 alkyl), carboxyl, C1-8 alkoxycarbonyl, nitro, cyano, halogen atom, C1-6 acyl (*e.g.* formyl, ethanoyl, propanoyl, butanoyl, pentanoyl, hexanoyl *etc.*), oxo or oxo. It more preferably means C1-4 alkyl (*e.g.* methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, *sec*-butyl *etc.*), C1-4 alkoxycarbonyl (*e.g.* methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl *etc.*), methoxy, isopropoxy, trifluoromethyl, trifluoromethoxy, difluoromethoxy, halogen atom, cyano, pyridinyl, oxo, phenoxy, phenyl which may be substituted with 1-3 R³(s) and cyclohexyl. It further preferably means methyl, *tert*-butyl, phenyl which may be substituted with 1-3 R³(s), *tert*-butoxycarbonyl and benzyl.

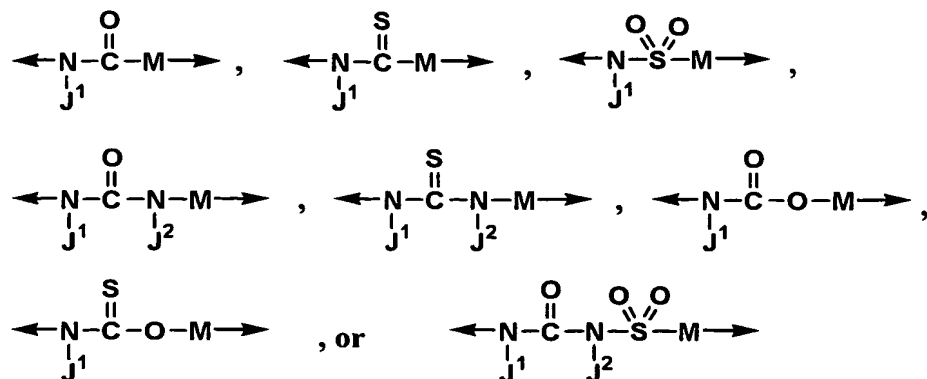
“Cyclic group” in “cyclic group which may have a substituent(s)” represented by Q preferably means C3-10 mono- or bi-carbocyclic ring, or 3-10 membered heterocyclic ring containing 1 to 5 hetero atom(s) selected from oxygen atom(s), nitrogen atom(s) and/or sulfur atom(s). It more preferably means benzene, cyclohexane, pyridine, 1,3-thiazole, furan, pyrazole, imidazole, thiophene, tetrahydrothiophene, tetrahydropyran, 1,3-benzodioxol, isoxazole or 1-benzothiophene. It particularly preferably means benzene.

“Hydrocarbon group” in “hydrocarbon group which may have a substituent(s)” represented by Q preferably means C1-8 alkyl.

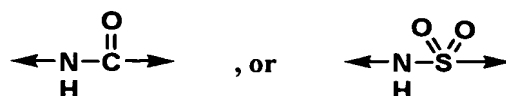
“Hydrocarbon group which may have a substituent(s)” represented by Q preferably means methyl, trifluoromethyl, ethyl, benzyl, phenoxymethyl and benzyloxymethyl. It more preferably means methyl, ethyl, benzyl and phenoxymethyl.

“Substituent” in “cyclic group which may have a substituent(s)” represented by Q preferably means methyl, trifluoromethyl, methoxy, trifluoromethoxy, difluoromethoxy, trifluoroethyl and halogen atom. It more preferably means methyl, trifluoromethyl, methoxy, trifluoromethoxy, difluoromethoxy and chlorine atom.

E preferably means a spacer of which main chain has an atom number of 1-4 containing of hydrogen-bond acceptor site. It more preferably means



(wherein, all symbols have the same meanings as the described above.). It further means



5 T^{IA} preferably means *tert*-butyl, sec-butyl, isobutyl, isopropyl, isopentyl or neopentyl.

Ring G preferably means mono-carbocyclic ring and mono-heterocyclic ring. Concretely, it means benzene, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, pyran, tetrahydropyran, furan, pyridine, pyrrole, thiophene, tetrahydrothiophene, imidazole, pyrazole, 1,3-thiazole, 1,3-benzodioxol, 1-benzothiophene, isothiazole, oxazole, isoxazole, pyrimidine, pyrazine, pyridazine, triazole and tetrazole. It particularly preferably means benzene.

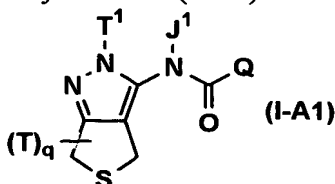
J^1 preferably means hydrogen atom, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, phenyl, benzyl, benzoyl or thiophenecarbonyl.

15 J^2 preferably means hydrogen atom.

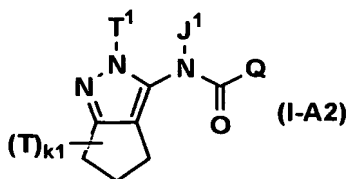
M preferably means binding bond, methylene or ethylene.

L^1 preferably means nitrogen atom, sulfur atom, methylene or ethylene.

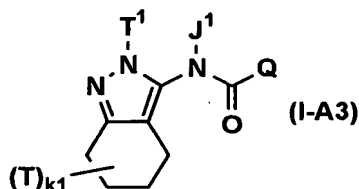
Among the compounds represented by formula (I), preferable compounds mean the compound represented by formula (I-A1)



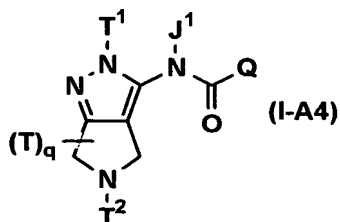
20 (wherein, q is 0 or an integer of 1-4, the other symbols have the same meanings as the described above.), the compound represented by formula (I-A2)



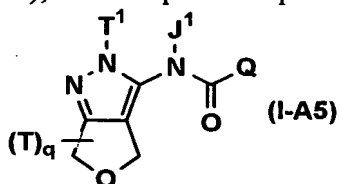
(wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-A3)



- 5 (wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-A4)

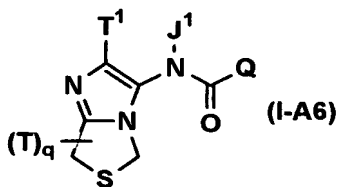


(wherein, T² is a hydrogen atom or a substituent, the other symbols have the same meanings as the described above.), the compound represented by formula (I-A5)

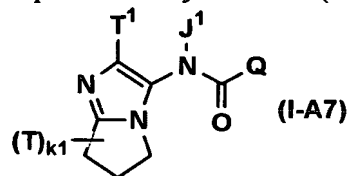


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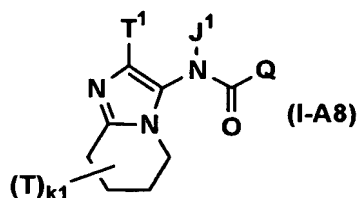
(wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-A6)



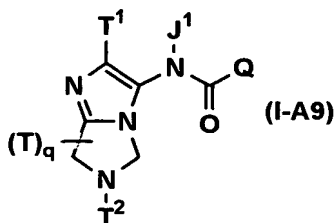
- 15 (wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-A7)



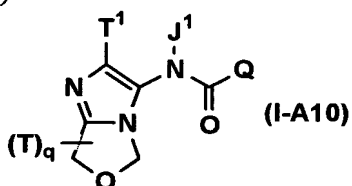
(wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-A8)



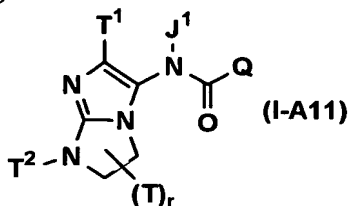
5 (wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-A9)



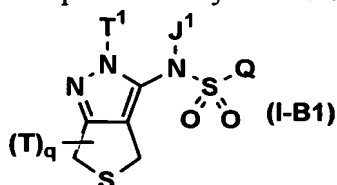
(wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-A10)



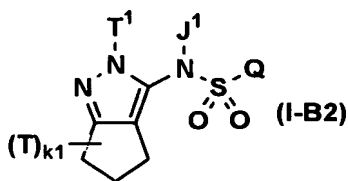
10 (wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-A11)



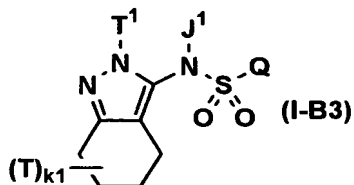
(wherein, r is 0 or an integer of 1-3, the other symbols have the same meanings as the described above.), the compound represented by formula (I-B1)



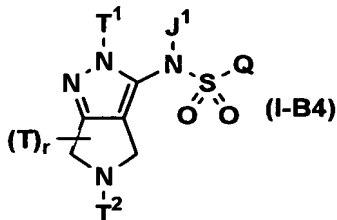
15 (wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-B2)



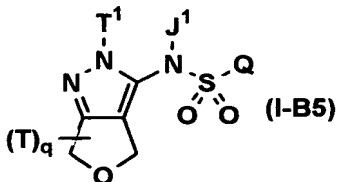
(wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-B3)



- 5 (wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-B4)

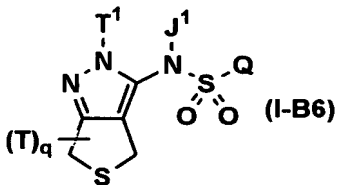


(wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-B5)



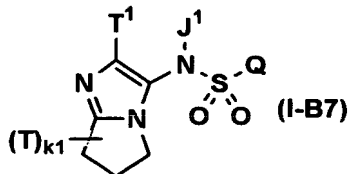
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(wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-B6)

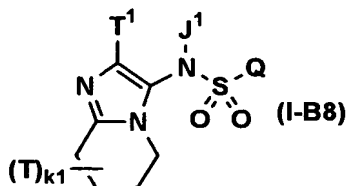


(wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-B7)

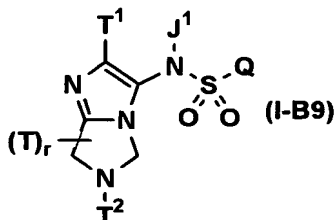
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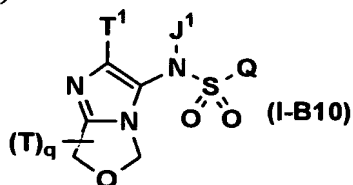
(wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-B8)



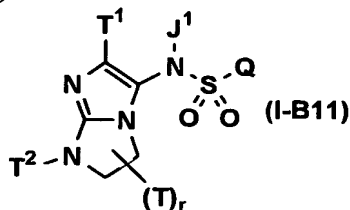
5 (wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-B9)



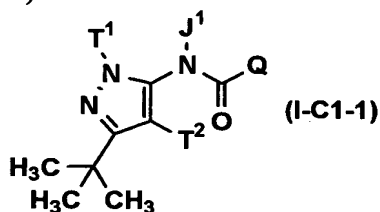
(wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-B10)



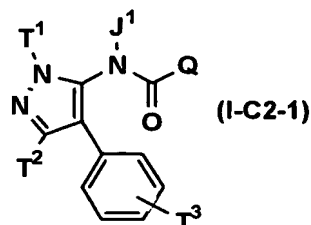
10 (wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-B11)



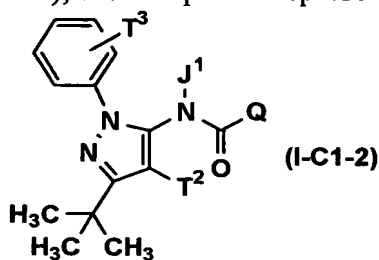
(wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-C1-1)



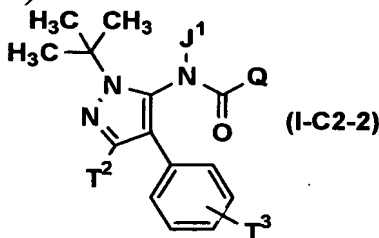
15 (wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-C2-1)



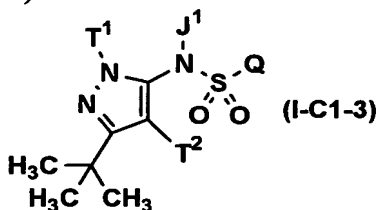
(wherein, T³ is a hydrogen atom or a substituent, the other symbols have the same meanings as the described above.), the compound represented by formula (I-C1-2)



- 5 (wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-C2-2)

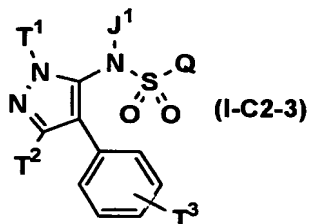


(wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-C1-3)

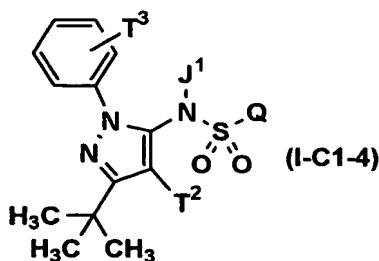


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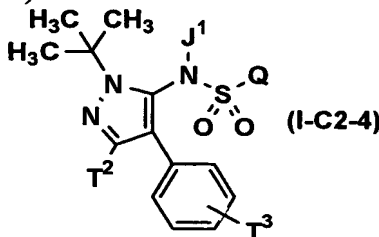
(wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-C2-3)



- 15 (wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-C1-4)



(wherein, all symbols have the same meanings as the described above.), the compound represented by formula (I-C2-4)



- 5 (wherein, all symbols have the same meanings as the described above.), a salt thereof, an N-oxide thereof, a solvate thereof, or a prodrug thereof. More preferable compounds mean the compounds shown in Examples and the following compounds.
- (1) N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)propanamide (manufactured by IF Ltd.; Cat. No. F0396-0004),
- 10 (2) N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)-2-methylpropanamide (manufactured by IF Ltd.; Cat. No. F0396-0009),
- (3) 3-bromo-N-[2-(4-chlorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]benzamide (manufactured by IF Ltd.; Cat. No. F0396-0085),
- (4) 4-bromo-N-[2-(4-chlorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]benzamide (manufactured by IF Ltd.; Cat. No. F0396-0090),
- 15 (5) N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)-3,5-dichlorobenzamide (manufactured by IF Ltd.; Cat. No. F0396-0119),
- (6) N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)-3-(trifluoromethyl)benzamide (manufactured by IF Ltd.; Cat. No. F0396-0305),
- 20 (7) N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)-3-methylbutanamide (manufactured by IF Ltd.; Cat. No. F0396-0344),
- (8) N-{[(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)amino]carbonyl}-4-methylbenzenesulfonamide (manufactured by IF Ltd.; Cat. No. F0396-0462),
- 25 (9) N-[2-(3-methylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-(trifluoromethyl)benzamide (manufactured by IF Ltd.; Cat. No. F0453-0476),

- (10) N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)-2-(trifluoromethyl)benzamide (manufactured by IF Ltd.; Cat. No. F0453-0506),
- (11) N-[2-(2-methylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-(trifluoromethyl)benzamide (manufactured by IF Ltd.; Cat. No. F0778-0139),
- 5 (12) N-[2-(4-methylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-(trifluoromethyl)benzamide (manufactured by IF Ltd.; Cat. No. F0778-0140),
- (13) N-[2-(2-methylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-3-(trifluoromethyl)benzamide (manufactured by IF Ltd.; Cat. No. F0778-0145),
- (14) N-[2-(4-methylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-3-
- 10 (trifluoromethyl)benzamide (manufactured by IF Ltd.; Cat. No. F0778-0146),
- (15) (2E)-N-[2-(4-chlorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-3-phenylacrylamide (manufactured by IF Ltd.; Cat. No. F0396-0019),
- (16) (2E)-N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)-3-phenylacrylamide (manufactured by IF Ltd.; Cat. No. F0396-0021),
- 15 (17) N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)-1,1'-biphenyl-4-carboxamide (manufactured by IF Ltd.; Cat. No. F0396-0161),
- (18) N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)-1-naphthamide (manufactured by IF Ltd.; Cat. No. F0396-0201),
- (19) N-[2-(4-chlorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-(1-
- 20 naphthyl)acetamide (manufactured by IF Ltd.; Cat. No. F0396-0204),
- (20) 4-benzyl-N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)benzamide (manufactured by IF Ltd.; Cat. No. F0396-0257),
- (21) N-[2-(3-methylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-1,1'-biphenyl-4-carboxamide (manufactured by IF Ltd.; Cat. No. F0396-0389),
- 25 (22) N-[2-(3-methylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-naphthamide (manufactured by IF Ltd.; Cat. No. F0453-0472),
- (23) N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)-2-naphthamide (manufactured by IF Ltd.; Cat. No. F0453-0502),
- (24) N-[2-(2-methylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-3-
- 30 phenylpropanamide (manufactured by IF Ltd.; Cat. No. F0529-0055),
- (25) 2-(4-fluorophenyl)-N-[2-(2-methylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]acetamide (manufactured by IF Ltd.; Cat. No. F0529-0059),
- (26) N-[2-(4-methylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-3-phenylpropanamide (manufactured by IF Ltd.; Cat. No. F0529-0085),
- 35 (27) 2-(4-fluorophenyl)-N-[2-(4-methylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]acetamide (manufactured by IF Ltd.; Cat. No. F0529-0089),

- (28) N-[2-(4-chlorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-(4-fluorophenyl)acetamide (manufactured by IF Ltd.; Cat. No. F0529-0119),
- (29) N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)-3-phenylpropanamide (manufactured by IF Ltd.; Cat. No. F0529-0130),
- 5 (30) N-[2-(4-methylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-phenylbutanamide (manufactured by IF Ltd.; Cat. No. F0541-1232),
- (31) 4-butyl-N-[2-(3-chlorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]cyclohexanecarboxamide (manufactured by IF Ltd.; Cat. No. F0541-1247),
- (32) N-[2-(3-chlorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-phenylbutanamide (manufactured by IF Ltd.; Cat. No. F0541-1314),
- 10 (33) N-[2-(3-chlorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-3-phenylpropanamide (manufactured by IF Ltd.; Cat. No. F0541-1315),
- (34) N-[2-(4-chlorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-phenylbutanamide (manufactured by IF Ltd.; Cat. No. F0541-1344),
- 15 (35) N-[2-(4-fluorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]pentanamide (manufactured by IF Ltd.; Cat. No. F0541-1365),
- (36) 4-butyl-N-[2-(4-fluorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]cyclohexanecarboxamide (manufactured by IF Ltd.; Cat. No. F0541-1373),
- (37) N-[2-(2,3-dimethylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-phenylacetamide (manufactured by IF Ltd.; Cat. No. F0541-1546),
- 20 (38) N-[2-(2,3-dimethylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-(4-fluorophenyl)acetamide (manufactured by IF Ltd.; Cat. No. F0541-1548),
- (39) N-[2-(2,3-dimethylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-phenylbutanamide (manufactured by IF Ltd.; Cat. No. F0541-1552),
- 25 (40) N-[2-(2,3-dimethylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-3-phenylpropanamide (manufactured by IF Ltd.; Cat. No. F0541-1553),
- (41) N-[2-(2,4-dimethylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-phenylbutanamide (manufactured by IF Ltd.; Cat. No. F0541-1680),
- (42) N-[2-(3,5-dimethylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-methylbenzamide (manufactured by IF Ltd.; Cat. No. F0778-0011),
- 30 (43) N-[2-(2,4-dimethylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-1-naphthamide (manufactured by IF Ltd.; Cat. No. F0778-0250),
- (44) 4-butyl-N-[2-(4-methylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]cyclohexanecarboxamide (manufactured by IF Ltd.; Cat. No. F0778-0392),
- 35 (45) N-[2-(2,4-dimethylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-phenylacetamide (manufactured by IF Ltd.; Cat. No. F0778-0412).

Preferable compounds for preparing the composition of a preventive and/or therapeutic agent for a mitochondrial benzodiazepine receptor mediated disease include all compounds of the present invention showed in Examples.

5 [Isomer]

Unless otherwise specified, all isomers are included in the present invention. For example, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylene, alkenylene, alkynylene, alkylidene and alkenylidene group means straight-chain or branched-chain ones. In addition, isomers on double bond, ring, fused ring (E-, Z-, cis-, trans-isomer), isomers
10 generated from asymmetric carbon atom(s) (R-, S-isomer, α -, β -configuration, enantiomer, diastereomer), optically active isomers (D-, L-, d-, l-isomer), polar compounds generated by chromatographic separation (more polar compound, less polar compound), equilibrium compounds, rotational isomers, mixtures thereof at voluntary ratios and racemic mixtures are also included in the present invention.

15 Optically-active compounds in the present invention may not only be 100% pure but also include below 50% of the other optically-compounds.

[Salt, N-oxide and solvate]

The salts of the compounds represented by formula (I) include all of
20 pharmaceutically acceptable ones. As pharmaceutically salts, non-toxic, water-soluble salts are preferred. The suitable salts include for example, salts of alkali metals (*e.g.*, potassium, sodium, lithium, *etc.*), salts of alkaline earth metals (*e.g.*, calcium, magnesium, *etc.*), ammonium salts (*e.g.*, tetramethylammonium salt, tetrabutylammonium salt, *etc.*), pharmaceutical acceptable salts of organic amine (*e.g.*,
25 triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)methylamine, lysine, arginine, N-methyl-D-glucamine, *etc.*), acid addition salts (salts of inorganic acids (*e.g.*, hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, nitrate *etc.*), and salts of organic acids (*e.g.*, acetate, trifluoroacetate,
30 lactate, tartrate, oxalate, fumarate, maleate, benzoate, citrate, methanesulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate, isethionate, glucuronate, gluconate *etc.*).

In addition, N-oxide of the compound represented by formula (I) means
35 the compound in the present invention may be the above-mentioned salts of alkali (earth) metals, ammonium salts, salts of organic amine, acid addition salts and so on.

The suitable solvates of the compound represented by formula (I) include for example, hydrates, solvates of the alcohols (*e.g.*, ethanol *etc.*), and so on. The solvates are preferably nontoxic and water-soluble. In addition, the solvate of the compound in the present invention included the solvate of salts of alkali (earth) metals, ammonium salts, salts of organic amine, acid addition salts, N-oxide and so on of the above-mentioned compound of the present invention.

The compound of the present invention may be converted into the above-mentioned salt, the above-mentioned N-oxide, the above-mentioned solvates by known methods.

[Prodrug]

The prodrug of the compounds represented by formula (I) means a compound is the compound represented by formula (I) by reaction with enzymes, gastric acids and so on within an organism. The prodrug of the compounds represented by formula (I) include, when the compounds represented by formula (I) have amino, the prodrug is the compounds the amino of which is acylated, alkylated, phosphorylated (*e.g.*, the compounds are that the amino of the compounds represented by formula (I) is eicosanoated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolan-4-yl)methoxycarbonylated, tetrahydrofuranated, pyrrolidylmethylated, pivaloyloxymethylated, acetoxymethylated, *tert*-butylated, *etc.*); when the compounds represented by formula (I) have hydroxyl, the prodrug is the compounds the hydroxyl of which are acylated, alkylated, phosphorylated, borated (*e.g.*, the compounds are that the hydroxyl of the compounds represented by formula (I) are acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated, dimethylaminomethylcarbonylated *etc.*); when the compounds represented by formula (I) have carboxyl, the prodrug is the compound the carboxyl of which are esterified, amidated (*e.g.*, the compounds are that the carboxyl of the compounds represented by formula (I) is ethylesterified, phenylesterified, carboxymethylesterified, dimethylaminomethylesterified, pivaloyloxymethylesterified, ethoxycarbonyloxyethylesterified, phthalidylesterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methylesterified, cyclohexyloxycarbonylethylesterified, methylamidated *etc.*); and so on. These compounds can be prepared by known methods. In addition, the prodrug of the compound represented by formula (I) may be either hydrate or non-hydrate. In addition, the prodrug of the compound represented by formula (I) may be converted into the compound represented by formula (I) under the physiological condition which is described in "the development of medicine" vol.7 "molecular design" published in 1991

Hirokawa shoten p.p. 163-198. Further, the compound represented by formula (I) may be labeled with isotopes (*e.g.* ^3H , ^{14}C , ^{35}S , ^{125}I *etc.*) and so on.

[Pharmacological activity]

5 As pharmacological test other than one described in Examples, for example, there are the methods as follows.

Determination of pregnenolone in rat adrenocortical mitochondria:

10 The steroid productivity of the compound in the present invention can be evaluated using rat adrenocortical mitochondria.

 After intraperitoneal administration of 20mg/mL cycloheximide solution (1mL) to male SD rats, 10IU/mL adrenocorticotrophic hormone (ACTH) solution (0.3mL) is intraperitoneally administered to them in five minutes. 20 minutes after ACTH administration, the rats are sacrificed by cervical dislocation and bilateral
15 adrenal cortexes are removed at once. The removed adrenal cortexes are homogenized in buffer A (composition: 50mmol/L Tris-HCl; 250mmol/L sucrose) and then the suspension is centrifuged at 2000g for 3 minutes at 4 °C. The obtained supernatant is centrifuged at 12500g for 10 minutes at 4 °C. The pellet is washed with buffer A twice and suspended in buffer B (composition: 250mmol/L sucrose; 10mmol/L potassium
20 phosphate buffer; 15mmol/L triethanolamine; 20mmol/L potassium chloride; 5mmol/L magnesium chloride; 10 $\mu\text{mol/L}$ trilostane; 10 $\mu\text{mol/L}$ SU10603) for experiments. Assay buffer which includes malic acid (150mmol/L), $\beta\text{-NADP}^+$ (5mmol/L) and the compound in the present invention is incubated for 5 minutes at 37 °C. Then, crude mitochondrial membrane fraction derived from rat adrenal cortex is added and further
25 incubated for 10 minutes at 37 °C to produce pregnenolone (final concentration of the compound: 1 $\mu\text{mol/L}$). After incubation, the reaction is terminated by addition of ethanol, extracted by addition of n-hexane and then evaporated to dryness. The residue is dissolved in buffer C (composition: 0.1% gelatin; phosphate buffered salts solution), centrifuged and then the collected supernatant is determined as samples for
30 measurement. [^3H] pregnenolone (10000cpm; 100 μL), anti-pregnenolone antibody (ICN Biomedicals Inc; 100 μL) and sample (100 μL) are mixed and incubated overnight at 4 °C. After the reaction, the mixture is added by dextran/charcoal (200 μL), mixed well, kept on ice for 10 minutes and then centrifuged. The radioactivity of the supernatant is measured by liquid scintillation counter. The pregnenolone in the
35 sample is calculated from the standard curve.

Effect of the compound in the present invention on increase in pregnenolon content in the brain by loading stressor:

It can be confirmed that MBR antagonist can inhibit steroid production in the brain, as follows.

5 Male Wistar rats are loaded with psychological stressor (*Brain Res.*, 641, 21-28 (1994)). Water is stored up to about 10cm depth in a container of which the platform is set up at the center. Rats in the non-treated group are loaded without administration and stressor. In contrast, rats in the stressor loaded group are orally administered with the vehicle or the compounds and 30 minutes later the rats are put on
10 the platform to be loaded with stressor. One hour later from starting to load, the rats are irradiated by microwave (output: about 6.5kW, exposure time: 0.96s) using microwave applicator (Muromachi Kikai Co., Ltd.) and then the bilateral hippocampuses are removed and weighed. The hippocampuses are crushed, added by internal standard substance (D₄-pregnenolone 20ng), water (1mL) and diethylether/n-hexane (9:1, 3mL) and stirred. The mixture is crushed by ultrasonic waves, stirred
15 again, centrifuged at 3000rpm for 5 minutes and the organic layer is transferred to new tube with Pasteur pipet. The water phase is extracted with diethylether/n-hexane (9:1, 3mL) again and the organic layer is mixed to the above-mentioned extract. After reduced pressure to dryness, the residue is dissolved with 150μL water/acetonitrile (1:9)
20 again and measured by liquid chromatography/mass spectrometry (LC-MS). The measurement condition is shown as follows.

LC (Liquid chromatography):	Hewlett Packard series 1100,
Column:	Inertsil ODS-3, 3μm, 2,1 ^φ ×100mm,
Temperature:	room temperature,
25 Mobile phase:	5mmol/L CH ₃ CO ₂ NH ₄ /MeCN (10:90),
Flow rate:	0.2mL/min,
Injection volume:	40μL,
MS (Micro spectrometry):	Quattro II (Micromass),
Ionization mode:	Atmosphere Pressure Chemical Ionization
30 positive; Corona:	(APCI),
Sheath gas:	3.4kV,
Source temperature:	N ₂ (50L/hr),
Probe temperature:	180 °C,
35 Detection: Pregnenolone:	550 °C,
D ₄ -pregnenolone:	m/z 317.2 (cone: 10V),
	m/z 321.2 (cone: 10V).

Measurement of anti-stress effects:

Psychological stress is loaded to male Wistar rats (Brain research, 641, 21-28, 1994). Water is stored up to the depth of about 10cm in a container where the platform is set at the center. A stressor begins to load to rats 30 minutes after the vehicle or the compound in the present invention is orally administered. The number of defecation is counted 1 hour later (e.g. 10 per each group). By comparing feces of the group which is administered with the compounds of the present invention to the group without treatment, the anti-stress effects of the compounds of the present invention can be evaluated.

Measurement of the anti anxiety activity with elevated plus-maze

The elevated plus-maze apparatus is set up to cross two opened arms of same length (50×10cm) and two closed arms (40cm walls are set up) of same length (50×10cm) at right angles each other 50cm in height from floor. The light is set up to keep a regular intensity of illumination in the both opened arms.

Male SD rats administered orally with the various concentrations of the compounds of the present invention (5mL/kg) are stood still at the center of the apparatus before 30 minutes of the evaluation and staying time (sec) of rats in the opened arms is measured for 5 minutes. Experimenters measure the time at fixed position during evaluation.

By comparing the staying time (sec) in the opened arms of the group which is administered with the compound of the present invention to the group without treatment, the anti anxiety activity of the present invention can be evaluated.

Measurement of the anti anxiety activity by Vogel conflict test:

The operant chamber (29×29×13cm, Med Associates Inc.) with metal grid floor, drinking nozzle and house light is used for the test. In the test, male SD rats are used and are kept thirsty for 48 hours before the evaluation.

Rats administered orally with the various concentrations of the compounds of the present invention (5mL/kg) are put on metal grid floor of the operant chamber before 30 minutes of the evaluation. The number of times of suffering shock is measured for 5 minutes under the condition where rats are suffered electro-shock of 0.65mA for 500 milliseconds each time rats drink for 2 seconds. As well, electro-shock and drinking behavior of rats are regulated by MED-PC software version 4.0 (Med Associates Inc.) to be recorded.

By comparing the number of times of suffering shock in the group which is administered with the compound of the present invention to the group without treatment, the anti anxiety activity of the present invention can be evaluated.

5 Measurement of the anti anxiety activity by social interaction test

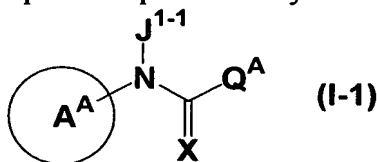
In the test, male SD rats reared separately are used. Two rats administered orally with various concentrations of the compounds of the present invention (5mL/kg) before 30 minutes of evaluation are put into the acrylic observation box (50×50×30cm). And then, they are observed for 10 minutes and the time of social interaction action such as smelling, tracking, grooming, riding on other rat, going under other rat *etc.*, is measured.

By comparing the time of social interaction in the group which is administered with the compound of the present invention to the group without treatment, the anti anxiety activity of the compounds of the present invention can be evaluated.

[Processes for the preparation of the compound in the present invention]

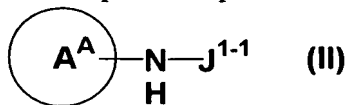
The compound in the present invention represented by formula (I) can be prepared by combining the known processes, for example, the following processes or the processes shown in Examples, which is the properly improved processes described in "*Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd Edition", "Richard C. Larock, John Wiley & Sons Inc, 1999". Still, ingredients may be used as salts in the following each processes for the preparation. As these salts, the salts described as the pharmaceutically acceptable ones in the above-mentioned formula (I) can be used.

[A] Among the compounds represented by formula (I), the compound wherein E is $-NJ^1-C(=X)-$, that is, the compound represented by formula (I-1)

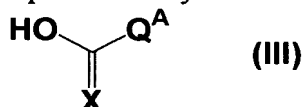


(wherein, X is an oxygen atom or a sulfur atom, J^{1-1} , A^A and Q^A have the same meanings as the above described J^1 , A and Q, respectively. But carboxyl, hydroxyl, amino or mercapto included the group represented by J^{1-1} , A^A and Q^A are, if necessary, protected. The other symbols have the same meanings as the described above.) can be prepared by the following methods of 1), 2) or 3).

1) The compound represented by formula (I-1) can be prepared by treating with (thio)amidation of the amine compound represented by formula (II)



(wherein, all symbols have the same meanings as the described above.) and the (thio)carboxylic acid compound represented by formula (III)



(wherein, all symbols have the same meanings as the described above.), if necessary, followed by subjecting to a deprotection reaction of protection group.

The (thio)amidation includes, for example, the method (1) using acid halide, (2) using mixed acid anhydride, (3) using condensing agent *etc.*

These methods are explained concretely as follows.

(1) The method using acid halide is carried out, for example by reacting the compound represented by formula (III) in an organic solvent (*e.g.* chloroform, dichloromethane, diethylether, tetrahydrofuran, dimethoxyethane *etc.*) or the absence of solvent, with acid halide agent (*e.g.* oxalylchloride, thionylchloride *etc.*) at the temperature from -20 °C to reflux temperature, and reacting the obtained acid halide with the compound represented by formula (II) in a organic solvent (*e.g.* chloroform, dichloromethane, diethylether, tetrahydrofuran, acetonitrile, ethyl acetate *etc.*) or the absence of solvent, under the presence of a base (*e.g.* pyridine, triethylamine, dimethylaniline, dimethylaminopyridine, diisopropylethylamine *etc.*) at the temperature of from -20 °C to reflux temperature. In addition, it is carried out by reacting the obtained halide with the compound represented by formula (II) in an organic solvent (*e.g.* dioxane, tetrahydrofuran, dichloromethane *etc.*), under the presence or absence of phase-transfer catalyst (*e.g.* quaternary ammonium salt *etc.*, for example, tetrabutylammonium chloride, triethylbenzylammonium chloride, tri n-octylmethylammonium chloride, trimethyldecylammonium chloride, tetramethylammonium bromide and so on.), using alkaline solution (*e.g.* sodium bicarbonate or sodium hydroxide solution *etc.*) at the temperature from -20 °C to reflux temperature.

(2) The method using mixed acid anhydride is carried out, for example the compound represented by formula (III) with an acid halide (*e.g.* pivaloyl chloride, tosyl chloride, mesyl chloride *etc.*), or an acid derivative (*e.g.* chloroethyl formate, chloroisobutyl formate *etc.*) in an organic solvent (*e.g.* chloroform, dichloromethane,

diethylether, tetrahydrofuran *etc.*) or the absence of solvent, under the presence of a base (*e.g.* pyridine, triethylamine, dimethylaniline, dimethylaminopyridine, diisopropylethylamine *etc.*) at the temperature from -20 °C to reflux temperature, and by reacting the obtained mixed acid anhydride with the compound represented by formula

5 (II) in an organic solvent (*e.g.* chloroform, dichloromethane, diethylether, tetrahydrofuran *etc.*) at the temperature from -20 °C to reflux temperature.

(3) The method using condensing agent is carried out, for example by reacting the compound represented by formula (III) with the compound represented by formula (II) in an organic solvent (*e.g.* chloroform, dichloromethane, dimethylformamide, diethylether, tetrahydrofuran *etc.*), or in the absence of solvent, under the presence or

10 the absence of a base (*e.g.* pyridine, triethylamine, dimethylaniline, dimethylaminopyridine *etc.*) using the condensing agent (*e.g.* 1,3-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDC), 1,1'-carbonyldiimidazole (CDI), 2-chloro-1-methylpyridinium iodine, 1-

15 propanephosphonic acid cyclic anhydride (PPA) *etc.*), using or not using 1-hydroxybenzotriazole (HOBt) at the temperature from -20 °C to reflux temperature.

These reactions (1), (2) and (3) are all preferably carried out under the anhydrous condition in the presence of inert gases (argon, nitrogen *etc.*).

The deprotection reaction of a protective group for carboxyl, hydroxyl, amino, or mercapto is known, and it includes

20

- (1) deprotection reaction by alkaline hydrolysis,
 - (2) deprotection reaction under acidic conditions,
 - (3) deprotection reaction by hydrogenolysis,
 - (4) deprotection reaction of a silyl group,
 - 25 (5) deprotection reaction using metals,
 - (6) deprotection reaction using metal complexes,
- and so on.

These methods are described concretely as follows.

(1) The deprotection reaction by alkaline hydrolysis is, for example, carried out

30 in an organic solvent (*e.g.*, methanol, tetrahydrofuran, or dioxane *etc.*) using a hydroxide of an alkali metal (*e.g.*, sodium hydroxide, potassium hydroxide, or lithium hydroxide *etc.*), a hydroxide alkaline earth metal (*e.g.*, barium hydroxide, or calcium hydroxide *etc.*), or a carbonate (*e.g.*, sodium carbonate or potassium carbonate, *etc.*), or an aqueous solution thereof, or a mixture thereof at a temperature of -20°C to reflux

35 temperature.

(2) The deprotection reaction under acidic conditions is carried out, for example, in an organic solvent (*e.g.*, dichloromethane, chloroform, dioxane, ethyl acetate, or anisole *etc.*) in an organic acid (*e.g.*, acetic acid, trifluoroacetic acid, methansulfonic acid, or p-tosylate, *etc.*), or an inorganic acid (*e.g.*, hydrochloric acid, or sulfuric acid, *etc.*) or a mixture thereof (*e.g.*, hydrogen bromide/acetic acid, *etc.*), under the presence
5 or the absence of 2,2,2-trifluoroethanol at a temperature of -20°C to 100°C.

(3) The deprotection reaction by hydrogenolysis is carried out, for example, in a solvent (*e.g.*, ethers (*e.g.*, tetrahydrofuran, dioxane, dimethoxyethane, or diethylether, *etc.*), alcohols (*e.g.*, methanol, or ethanol, *etc.*), benzenes (*e.g.*, benzene, or toluene *etc.*),
10 ketones (*e.g.*, acetone, or methylethylketone, *etc.*), nitriles (*e.g.*, actetonitrile *etc.*), amides (*e.g.*, dimethylformamide *etc.*), water, ethyl acetate, acetic acid, or a mixed solvent of at least two of these *etc.*) in the presence of a catalyst (*e.g.*, palladium-carbon, palladium black, palladium hydroxide-carbon, platinum oxide, or Raney nickel, *etc.*) under the hydrogen atmosphere at normal pressure or under pressurization, or in the
15 presence of ammonium formate at a temperature of -20°C to 200°C.

(4) The deprotection reaction of a silyl group is carried out, for example, in a water-miscible organic solvent (*e.g.*, tetrahydrofuran, or acetonitrile, *etc.*) using tetrabutylammonium fluoride at a temperature of -20°C to reflux temperature.

(5) The deprotection reaction using metals is carried out, for example, in an
20 acidic solvent (*e.g.*, acetic acid, pH4.2-7.2 buffer solution, or a mixture of a solution thereof and an organic solvent of tetrahydrofran *etc.*) in the presence of zinc powder, if necessary sonicating, at the temperature of -20°C to reflux temperature.

(6) The deprotection reaction using metal complexes is carried out, for example, in an organic solvent (*e.g.*, dichloromethane, dimethylformamide, tetrahydrofuran, ethyl
25 acetate, acetonitrile, dioxane, ethanol *etc.*), water, or a mixture thereof, in the presence of a trap reagent (*e.g.*, tributyltine hydride, triethylsilane, dimedone, morpholine, diethylamine, pyrrolidine, *etc.*), an organic acid (*e.g.*, acetic acid, formic acid, 2-ethyl hexanoic acid, *etc.*) and/or salts of organic acid (*e.g.*, sodium 2-ethylhexanoate, potassium 2-ethylhexanoate *etc.*), in the presence or absence of a phosphine reagent
30 (*e.g.*, triphenylphosphine *etc.*), using metal complexes (*e.g.*, tetrakistriphenylphosphinepalladium(0), dichlorobis(triphenylphosphine)palladium(II), palladium acetate(II), tris(triphenylphosphine)rhodium(I) chloride *etc.*) at the temperature of -20°C to reflux temperature.

In addition, the deprotection reaction except the above-mentioned processes
35 can be carried out, for example, by the process described in T.W. Greene, *Protective Groups in Organic Synthesis*, Wiley, New York, 1999.

The protection group for carboxyl includes, for example, methyl, ethyl, allyl, t-butyl, trichloroethyl, benzyl (Bn), phenacyl, p-methoxybenzyl, trityl, 2-chlorotrityl or structure thereof bound to solid phase carrier and so on.

5 The protection group for hydroxyl includes, for example, methyl, trytyl, methoxymethyl (MOM), 1-ethoxyethyl (EE), methoxyethoxymethyl (MEM), 2-tetrahydropyranyl (THP), trimethylsilyl (TMS), triethylsilyl (TES), t-butyldimethylsilyl (TBDMS), t-butyldiphenylsilyl (TBDPS), acetyl (Ac), pivaloyl, benzoyl, benzyl (Bn), p-methoxybenzyl, allyloxycarbonyl (Alloc), 2,2,2-trichloroethoxycarbonyl (Troc), and so on.

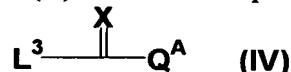
10 The protection group of amino includes benzyloxycarbonyl, t-butoxycarbonyl, allyloxycarbonyl (Alloc), 1-methyl-1-(4-biphenyl) ethoxycarbonyl (Bpoc), trifluoroacetyl, 9-fluorenylmethoxycarbonyl, benzyl (Bn), p-methoxybenzyl, benzyloxymethyl (BOM), 2-(trimethylsilyl) ethoxymethyl (SEM) and so on.

15 The protection group of mercapto includes, for example, benzyl, methoxybenzyl, methoxymethyl (MOM), 2-tetrahydropyranyl (THP), diphenylmethyl, acetyl (Ac) and so on.

20 The protective group for carboxyl, hydroxyl, amino or mercapto is not particularly limited to the above mentioned groups, so long as it can be easily and selectively left. For example, those described in T.W. Greene, *Protective Groups in Organic Synthesis*, Wiley, New York, 1999 can be used.

As will be easily understood by those skilled in the art, the intended compounds in the present invention can be easily prepared by choosing these deprotection reactions.

2) 25 The compound represented by formula (I-1) can be prepared by reacting the compound represented by formula (II) with the compound represented by formula (IV)



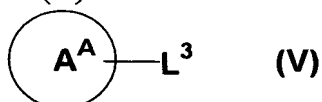
(wherein, L^3 is a leaving group such as halogen atom, imidazolyl *etc.*, the other symbols have the same meanings as the described above.), if necessary, followed by subjecting to a deprotection reaction of protection group.

30 The reaction with the compound represented by formula (II) and the compound represented by formula (IV) is carried out, for example, by reacting the compound represented by formula (IV) with the compound represented by formula (II) in an organic solvent (*e.g.* chloroform, dichloromethane, diethylether, tetrahydrofuran, acetonitrile, ethyl acetate *etc.*) in the presence of base (*e.g.* pyridine, triethylamine, dimethylaniline, dimethylaminopyridine, diisopropylethylamine *etc.*) at temperature 35 from -20 °C to reflux temperature. In addition, the reaction can be also carried out by

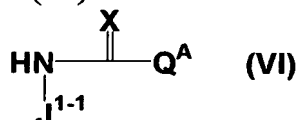
reacting the compound represented by formula (IV) and the compound represented by formula (II) in an organic solvent (*e.g.* dioxane, tetrahydrofuran, dichloromethane *etc.*) in the presence or absence of phase-transfer catalyst (*e.g.* quaternary ammonium salt *etc.*, such as tetrabutylammonium chloride, triethylbenzylammonium chloride, tri n-octylmethylammonium chloride, trimethyldecylammonium chloride, tetramethylammonium bromide and so on) using aqueous alkali solution (*e.g.* aqueous sodium hydrogen carbonate solution, sodium hydroxide solution *etc.*) at a temperature from -20 °C to reflux temperature.

The deprotection reaction of the protective group can be carried out by above described method.

3) The compound represented by formula (I-1) can be prepared by reacting the compound represented by formula (V)



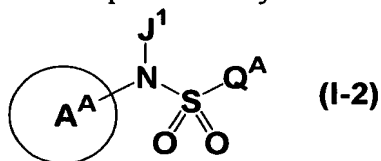
(wherein, all symbols have the same meanings as the described above.) with the compound represented by formula (VI)



(wherein, all symbols have the same meanings as the described above.), if necessary, followed by subjecting to a deprotection reaction of protection group.

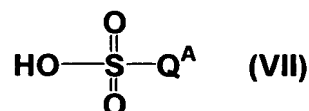
The reaction with the compound represented by formula (V) and the compound represented by formula (VI) can be carried out by pursuant method of the above described reaction with the compound represented by formula (II) and the compound represented by formula (IV).

[B] Among the compounds represented by formula (I), the compound wherein E is -NJ¹-SO₂-, that is, the compound represented by formula (I-2)



(wherein, all symbols have the same meanings as the described above.) can be prepared by the following methods of 1), 2) or 3).

1) The compound represented by formula (I-2) can be prepared by reacting the amine compound represented by formula (II) with the sulfonic acid compound represented by formula (VII)

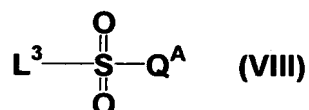


5 (wherein, all symbols have the same meanings as the described above.), if necessary, followed by subjecting to a deprotection reaction of protection group.

The reaction with the compound represented by formula (II) and the compound represented by formula (VII) includes, for example, the method (1) using acid halide, (2) using mixed acid anhydride, (3) using condensing agent *etc.* These methods can be carried out by pursuant the above described methods.

The deprotection reaction of the protective group can be carried out by above described method.

2) The compound represented by formula (I-2) can be prepared by reacting the compound represented by formula (II) with the compound represented by formula (VIII)

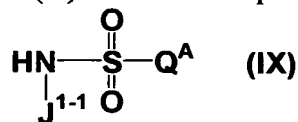


(wherein, all symbols have the same meanings as the described above.), if necessary, followed by subjecting to a deprotection reaction of protection group.

The reaction with the compound represented by formula (II) and the compound represented by formula (VIII) can be carried out by pursuant method of the above described reaction with the compound represented by formula (II) and the compound represented by formula (IV).

The deprotection reaction of the protective group can be carried out by above described method.

3) The compound represented by formula (I-2) can be prepared by reacting the compound represented by formula (V) with the compound represented by formula (IX)



(wherein, all symbols have the same meanings as the described above.), if necessary, followed by subjecting to a deprotection reaction of protection group.

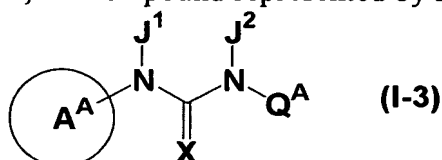
The reaction with the compound represented by formula (V) and the compound represented by formula (IX) can be carried out by pursuant method of the

above described reaction with the compound represented by formula (II) and the compound represented by formula (IV).

The deprotection reaction of the protective group can be carried out by above described method.

5

[C] Among the compounds represented by formula (I), the compound wherein Y is $-NJ^1-C(=X)-NJ^2-$, that is, the compound represented by formula (I-3)



(wherein, all symbols have the same meanings as the described above.) can be prepared by the following methods of 1) or 2).

1) The compound represented by formula (I-3) can be prepared by treating with urea reaction of the amine compound represented by formula (II) and the compound represented by formula (X)



(wherein, all symbols have the same meanings as the described above.), if necessary, followed by subjecting to a deprotection reaction of protection group.

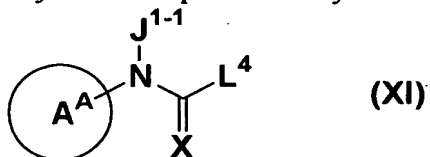
The urea reaction can be carried out by pursuant method of the following 1) or 2).

1) It can be carried out, for example, in an organic solvent (e.g. toluene, benzene, xylene, tetrahydrofuran, dichloromethane, diethylether, 1,2-dichloroethane, dimethylformamide *etc.*) at a temperature from 0 °C to reflux temperature.

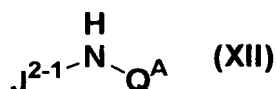
These reactions are preferably carried out under the anhydrous condition in the presence of inert gases.

The deprotection reaction of the protective group can be carried out by above described method.

2) The (thio)carbamoyl halide represented by formula (XI)



(wherein, L⁴ is a halogen atom, the other symbols have the same meanings as the described above.) and the amine compound represented by formula (XII)



(wherein, J^{2-1} has the same meanings as J^2 . But carboxyl, hydroxyl, amino or mercapto included the group represented by J^{2-1} is, if necessary, protected, the other symbols have the same meanings as the described above.), if necessary, followed by
 5 subjecting to a deprotection reaction of protection group.

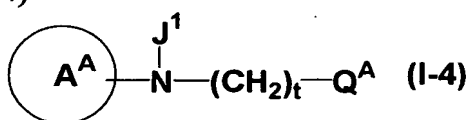
This reaction is known and it can be carried out by reacting the compound represented by formula (XI) with the compound represented by formula (XII) in an organic solvent (*e.g.* chloroform, dichloromethane, diethylether, tetrahydrofuran *etc.*) under the presence of a base (*e.g.* pyridine, triethylamine, dimethylaniline, dimethylaminopyridine, diisopropylethylamine *etc.*) at a temperature from -20°C to
 10 reflux temperature.

In addition, it can be also carried out by reacting the compound represented by formula (XI) with the compound represented by formula (XII) in an organic solvent (*e.g.* dioxane, tetrahydrofuran, diethylether *etc.*) using aqueous alkali solution (*e.g.* aqueous sodium hydrogen carbonate solution or sodium hydroxide *etc.*) at a temperature
 15 from -20°C to reflux temperature.

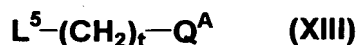
The compound represented by formula (XI) can be prepared by reacting the compound represented by formula (II) in an organic solvent (*e.g.* chloroform, dichloromethane, diethylether, tetrahydrofuran *etc.*) or absence of solvent under the
 20 presence of phosgene compound (*e.g.* phosgene, thiophosgene, triphosgene(bis(trichloromethyl)carbonate) *etc.*) and base (*e.g.* pyridine, triethylamine, dimethylaniline, dimethylaminopyridine, diisopropylethylamine *etc.*) at a temperature from -20°C to reflux temperature.

The deprotection reaction of the protective group can be carried out by
 25 above described method.

[D] Among the compounds represented by formula (I), the compound wherein Y is $-\text{N}(\text{J}^1)-(\text{CH}_2)_t-$ (wherein, t is an integer of 1 to 8.), that is, the compound represented by formula (I-4)



(wherein, all symbols have the same meanings as the described above.) can be prepared by reacting the amine compound represented by formula (II) with the compound represented by formula (XIII)

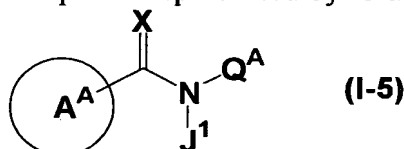


(wherein, L^5 is a leaving group, such as halogen atom, mesyloxy (OMs), tosyloxy (OTs), trifluoromethanesulfonyloxy (OTf), alkylthio, alkylsulfynyl, alkylsulfonyl, hydroxysulfonyl and so on, the other symbols have the same meanings as the described above.), if necessary, followed by subjecting to a deprotection reaction of protection group.

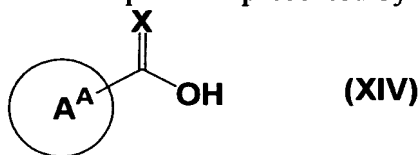
The reaction with the compound represented by formula (II) and the compound represented by formula (XIII) can be carried out in an organic solvent (e.g. tetrahydrofuran, dichloromethane, chloroform, benzene, toluene, xylene, hexane, heptane, cyclohexane, diethylether, dioxane, acetone, ethylmethylketone, acetonitrile, dimethylsulfoxide, dimethylformamide, dimethylacetamide, ethyl acetate *etc.*) under the presence of base (e.g. potassium carbonate, sodium carbonate, cesium carbonate, sodium halide *etc.*) and the presence or absence of catalyst (e.g. potassium iodide, sodium iodide, tetra-n-butylammonium iodide *etc.*) at a temperature from $-20\text{ }^{\circ}\text{C}$ to reflux temperature.

The deprotection reaction of the protective group can be carried out by above described method.

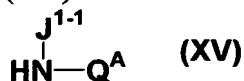
[E] Among the compound represented by formula (I), the compound wherein Y is $-\text{C}(=\text{X})-\text{N}(\text{J}^1)-$, that is, the compound represented by formula (I-5)



(wherein, all symbols have the same meanings as the described above.) can be prepared by treating with amidation of the compound represented by formula (XIV)



(wherein, all symbols have the same meanings as the described above.) and the compound represented by formula (XV)

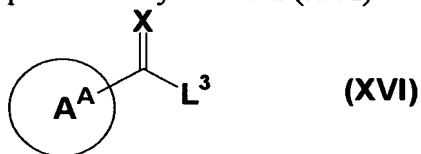


(wherein, all symbols have the same meanings as the described above.), if necessary, followed by subjecting to a deprotection reaction of protection group.

The amidation can be carried out by the same method as the above described reaction with the compound represented by formula (II) and the compound represented by formula (IV).

5 The deprotection reaction of the protective group can be carried out by above described method.

In addition, the compound represented by formula (I-5) can be also prepared by reacting the compound represented by formula (XVI)

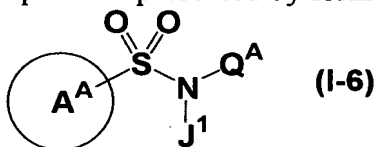


10 (wherein, all symbols have the same meanings as the described above.) with the compound represented by formula (XV), if necessary, followed by subjecting to a deprotection reaction of protection group.

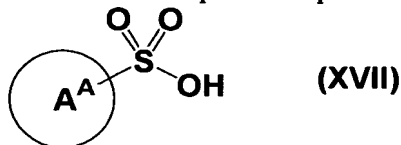
The reaction with the compound represented by formula (XVI) and the compound represented by formula (XV) can be carried out by the same method as the above described reaction with the compound represented by formula (II) and the compound represented by formula (III).

The deprotection reaction of the protective group can be carried out by above described method.

20 [F] Among the compounds represented by formula (I), the compound wherein Y is $-\text{SO}_2-\text{NJ}^1-$, that is, the compound represented by formula (I-6)



(wherein, all symbols have the same meanings as the described above.) can be prepared by treating with sulfonamidation of the compound represented by formula (XVII)

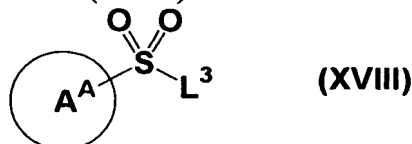


25 (wherein, all symbols have the same meanings as the described above.) and the compound represented by formula (XV), if necessary, followed by subjecting to a deprotection reaction of protection group.

Sulfonamidation can be carried out by the same method as described above.

The deprotection reaction of the protective group can be carried out by above described method.

2) The compound represented by formula (I-6) can be prepared by reacting the compound represented by formula (XVIII)

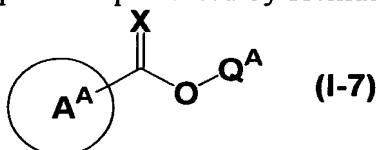


(wherein, all symbols have the same meanings as the described above.) and the compound represented by formula (XV), if necessary, followed by subjecting to a deprotection reaction of protection group.

The reaction with the compound represented by formula (XVIII) and the compound represented by formula (XV) can be carried out by the same method as the above described reaction with the compound represented by formula (II) and the compound represented by formula (IV).

The deprotection reaction of the protective group can be carried out by above described method.

[G] Among the compounds represented by formula (I), the compound wherein E is $-\text{C}(=\text{X})-\text{O}-$, that is, the compound represented by formula (I-7)



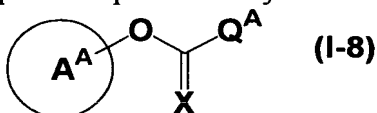
(wherein, all symbols have the same meanings as the described above.) can be prepared by treating with (thio)esterification of the compound represented by formula (XII) and the compound represented by formula (XIX)



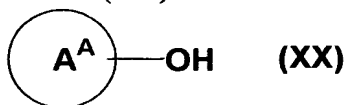
(wherein, all symbols have the same meanings as the described above.).

(Thio)esterification can be carried out by the same method as the above described (thio)amidation.

[H] Among the compounds represented by formula (I), the compound wherein E is $-\text{O}-\text{C}(=\text{X})-$, that is, the compound represented by formula (I-8)



(wherein, all symbols have the same meanings as the described above.) can be prepared by treating with (thio)esterification of the compound represented by formula (III) and the compound represented by formula (XX)

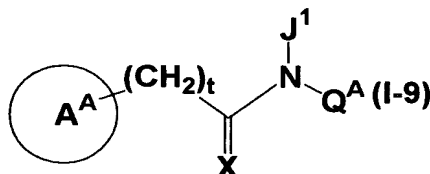


5 (wherein, all symbols have the same meanings as the described above.).

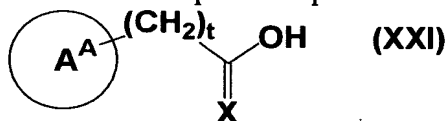
(Thio)esterification can be carried out by the same method as the above described (thio)amidation.

The compounds represented by the above described formula (I-1) to (I-8) all have only amide bond, ester bond or sulfonamide bond between ring A and Q.

10 However, besides these compounds, the compound which has alkylene as spacer between ring A and amide bond, for example, the compound represented by formula (I-9)



15 (wherein, all symbols have the same meanings as the described above.), as will be easily understood by the skilled person, can be prepared by treating with the same reaction as the above described amidation of the compound represented by formula (XXI)

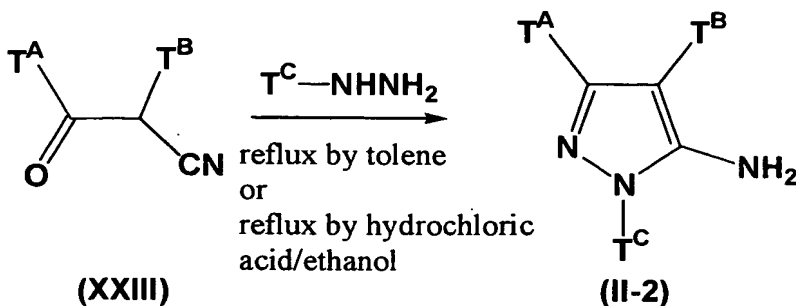


(wherein, all symbols have the same meanings as the described above.) and the compound represented by formula (XV).

20 The compounds represented by formula (II) to (XXI) used as starting materials or reagents are well known per se or can be easily prepared by the known processes, for example, processes described in "Comprehensive Organic Transformations:" or "Journal of Medicinal Chemistry, 45, 14, p. 2995 (2002)" and so on.

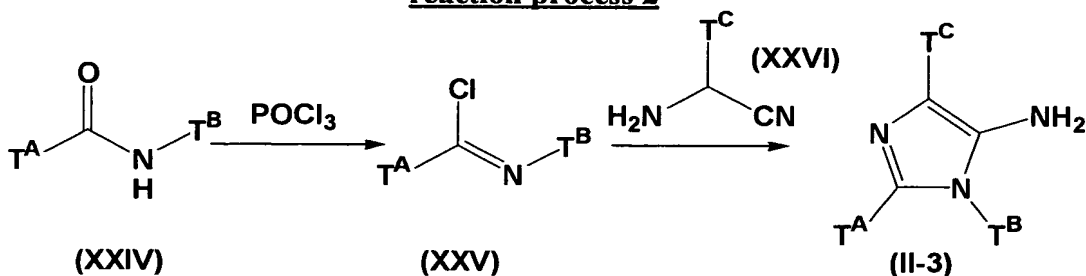
25 Among the compound represented by formula (II), for example, the compound having pyrazole skeleton can be prepared according to the method represented by reaction process 1. In the reaction process 1, T^A, T^B and T^C are each independently hydrogen atom or substituent (it has the same meanings as the substituent of ring A).

reaction process 1



Among the compound represented by formula (II), for example, the compound having imidazole skeleton can be prepared according to the method represented by reaction process 2.

reaction process 2



In the reaction process 1 and 2, the compounds represented by formula (XXIII), (XXIV) and (XXVI) used as starting materials or reagents are well known per se or can be easily prepared by the known processes.

In each reaction in the present specification, solid-phase supported reagent accordingly supported to macromolecule polymer (e.g. polystyrene, polyacrylamide, polypropylene, polyethyleneglycol *etc.*) may be used.

In each reaction in the present specification, reaction products may be purified in an ordinary manner, for example, through normal-pressure or reduced-pressure distillation, or through high-performance liquid chromatography with silica gel or magnesium silicate, thin-layer chromatography, or column chromatography, ion-exchange resin, scavenger resin or through washing or recrystallization and so on. The purification may be effected in each reaction or after some reactions.

[Toxicity]

Toxicity of the compound represented by formula (I) is very low, and it is safe enough to use as a pharmaceutical agent.

[Effect of the Invention]

Since the compounds of the present invention represented by formula (I), a salt thereof, an N-oxide thereof or a solvate thereof, or a prodrug thereof have the affinity to MBR, they are useful for the prevention and/or treatment for disease induced or exacerbated and/or reignited by stressor or useful for the prevention and/or treatment for disease caused by stress.

The disease induced or exacerbated and/or reignited by stressor or the disease caused by stress include, for example, central nervous system diseases caused by stress (*e.g.* anxiety related disease (neurosis, psychosomatic disorder, generalized anxiety disorder (GAD), social-anxiety disorder (SAD), panic disorder, hyperactivity disorder, attention-deficit, personality disorder, bipolar disorder, autism *etc.*), sleep disorder, depression, reactive depression, epilepsy, Parkinson's disease, Perkinsonian syndrome, schizophrenia, autonomic dystonia, Huntington's disease, Alzheimer's disease, affective disorder, cognitive disorder, migraine, tension headache, cluster headache, posttraumatic stress disorder, dissociative disorder, insomnia, nervous vomiting, nervous cough, psychogenic convulsive seizure, psychogenic syncopal attack, maladjustment to job, burn-out syndrome, chronic fatigue syndrome, writer's cramp, spastic torticollis, *etc.*), respiratory system diseases caused by stress (*e.g.* asthma, bronchial asthma, hyperventilation syndrome, laryngeal spasm, chronic obstructive pulmonary diseases, *etc.*), digestive system diseases caused by stress (*e.g.* irritable bowel syndrome, peptic ulcer, functional dyspepsia, gastric ulcer, duodenal ulcer, ulcerative colitis, biliary tract dyskinesia, esophageal spasm, gastric atony, aerophagy, chronic hepatitis, chronic pancreatitis, *etc.*), cardiovascular system diseases caused by stress (*e.g.* essential hypertension, arrhythmia, (neurological) angina pectoris, essential hypotension, orthostatic dysregulation, myocardial infarction, arteriosclerosis, vertigo *etc.*), uropathy-reproductive system diseases caused by stress (*e.g.* dysuria, nervous pollakisuria (hyperreflexic bladder), nocturia, enuresis, psychogenic ischuria, impotentia, prostatism, urethral syndrome *etc.*), gynecologic disorder caused by stress (*e.g.* menopausal disorder, menstrual pain, menstrual disorder, premenstrual syndrome, infertility, frigidity, serious vomiting of pregnancy, abortion, immature birth, *etc.*), endocrine and metabolic disease caused by stress (*e.g.* anorexia nervosa, eating disorder, anorexia, hyperphagia, Bartter's syndrome, hyperthyroidism, glucose metabolism disorder (*e.g.* diabetes, (reflex) hypoglycemia *etc.*), lipid metabolism disorder (*e.g.* hyperlipemia *etc.*), gout, osteoporosis, hypothalamus disease, pituitary gland disease, accessory thyroid gland disease, adrenal cortex/adrenal medulla disease, gonad disease, psychogenic polydipsia, adiposity and so on), ophthalmologic diseases caused by stress

(*e.g.* asthenopia, central retinitis, floaters, blepharospasm, primary glaucoma, vertigo *etc.*), otolaryngological diseases caused by stress (*e.g.* tinnitus, vertigo, psychogenic deafness, chronic sinusitis, allergic rhinitis, smell disorder, stuttering, aphonia, *etc.*), dental surgery and dentistry caused by stress (*e.g.* temporomandibular arthrosis, glossopharyngeal neuralgia, sudden glossodynia, stomatitis, toothache, ozostomia, abnormal salivation, bruxism *etc.*), surgical and orthopedic diseases caused by stress (*e.g.* postoperative abdominal neurosis, dumping syndrome, polysurgery, plastic postoperative neurosis, rheumatoid arthritis, low back pain, cervico-omo-brachial syndrome, stiff neck, fibrositis, polyarthralgia, systemic myalgia, gout, *etc.*), skin diseases caused by stress (*e.g.* chronic urticaria, atopic dermatitis, hyperhidrosis, eczema, skin pruritus, alopecia areata, *etc.*) and other diseases caused by stress (*e.g.* cancer, systemic lupus erythematosus *etc.*).

The compounds in the present invention may be administered in combination with other pharmaceutical preparations for the purpose of 1) complement and/or enhancement of preventing and/or treating effect of the compounds in the present invention, 2) improvement of dynamics/absorption and lowering of dose of the compounds in the present invention and/or 3) alleviation of side effect of the compounds in the present invention.

The compounds in the present invention and other pharmaceutical preparations may be administered in the form of formulation having these components incorporated in one preparation or may be administered in separate preparations. In the case where these pharmaceutical preparations are administered in separate preparations, they may be administered simultaneously or at different times. In the latter case, the compounds in the present invention may be administered before the other pharmaceutical preparations. Alternatively, the other pharmaceutical preparations may be administered before the compounds in the present invention. The method for the administration of these pharmaceutical preparations may be same or different.

The other pharmaceutical preparations may be low-molecular compounds. In addition, they may be macromolecular protein, polypeptide, polynucleotide (DNA, RNA, and gene), antisense, decoy, antibody or vaccine and so on. The dose of the other pharmaceutical preparations can be accordingly selected as a standard of clinical dose. Additionally, the compounding ratio of the compounds in the present invention and the other pharmaceutical preparations can be accordingly selected by the age and body weight of administering object, the administration method, the administration time, the object disease, the symptom, the combination *etc.* For example, the other pharmaceutical preparations may be used from 0.01 to 100 parts by weight relative to 1

part by weight of the compounds in the present invention. The other pharmaceutical preparations may be administered at appropriate ratio combining one or more arbitrarily selected from the homogeneous groups or heterogeneous groups as follows. The other pharmaceutical preparations do not only include ones which have ever been found but
5 ones which will be found from now based on the above-mentioned mechanism.

The other pharmaceutical preparations which may combine the compounds in the present invention include, for example, antianxiety drugs (*e.g.* benzodiazepine anxiolytics, thienodiazepine anxiolytics, non-benzodiazepine anxiolytics, serotonergic drugs, CRF antagonists, tachykinin NK₁ antagonists *etc.*), antidepressants (*e.g.* tricyclic
10 antidepressants, tetracyclic antidepressants, monoamine release drugs, monoamine oxidase inhibitors, monoamine reuptake inhibitors (SSRI, SNRI), CRF inhibitors, tachykinin NK₁ inhibitors, neurotensin antagonists *etc.*), antiparkinson drugs (*e.g.* anticholinergic drugs, dopamine agonists, monoamine oxidase inhibitors, *etc.*), schizophrenia drugs (*e.g.* dopamine antagonists, *etc.*), antiepileptic drugs (*e.g.* barbituric
15 acid series, hydantoin series *etc.*), anti vertigo drugs, asthmatic drugs (*e.g.* bronchodilators, α receptor agonists, β_2 receptor agonists, xanthine series, inhaled steroids, anticholinergic drugs, 5-lipoxygenase inhibitors *etc.*), peptic ulcer drugs (*e.g.* offensive factor inhibitors, antipeptic drugs, antacids, histamine-H₂ receptor antagonists, anti gastrin drugs, proton pump inhibitors, muscarine receptor inhibitors, anticholinergic
20 drugs, defensive factor enhancers, prostaglandin derivatives, *etc.*), gastrointestinal tract function regulators, gastrointestinal tract prokinetic drugs (*e.g.* intestinal remedies, CCK-A antagonists, neurotensin antagonists, opioid agonists, muscarine receptor inhibitors, 5-HT₄ agonists, 5-HT₃ antagonists *etc.*), antidiarrheals (*e.g.* antidiarrheal drugs, opioid μ receptor stimulators, *etc.*), evacuants (*e.g.* bulk laxatives, saline
25 laxatives, stimulant laxatives, affinity polyacrylic resin *etc.*), antihypertensive drugs (*e.g.* calcium antagonists, β receptor blockers, α_1 receptor blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, *etc.*), antiarrhythmic drugs (*e.g.* sodium inhibitors, β receptor blockers, potassium antagonists, calcium antagonists, *etc.*), cardiac stimulants (*e.g.* phosphodiesterase inhibitors, cardiac glycosides, β receptor
30 agonists *etc.*), dysuria remedies (*e.g.* frequent urination remedies, anticholinergic drugs, muscarine agonists (antagonists), tachykinin NK₁ antagonists, NK₂ antagonists, *etc.*) and so on.

The diseases on which the preventive and/or therapeutic effect works with the above described combination drugs are not especially limited. The diseases may
35 be those which compensate for and/or enhance the preventive and/or therapeutic effect of the compounds in the present invention.

The other pharmaceutical preparations to compensate and/or enhance for preventive and/or therapeutic effect on irritable bowel syndrome of the compounds in the present invention include, for example, antianxiety drugs (*e.g.* benzodiazepine anxiolytics, thienodiazepine anxiolytics, non-benzodiazepine anxiolytics, serotonergic drugs, CRF antagonists *etc.*), antidepressants (*e.g.* monoamine release drugs, monoamine oxidase inhibitors, monoamine reuptake inhibitors (SNRI, SSRI), CRF inhibitors, neurotensin antagonists, tricyclic antidepressants, tetracyclic antidepressants, *etc.*), anticholinergic drugs, gastrointestinal tract function regulators, gastrointestinal tract prokinetic drugs (*e.g.* intestinal remedies, CCK-A antagonists, neurotensin antagonists, opioid agonists, muscarine agonists, 5-HT₄ agonists, *etc.*), antidiarrheals (*e.g.* antidiarrheal drugs, opioid μ receptor stimulators, *etc.*), evacuants (*e.g.* bulk laxatives, saline laxatives, stimulant laxatives, affinity polyacrylic resin *etc.*), mucosal paralytic drugs, autonomic nerve modulators, calcium antagonists, phosphodiesterase inhibitors, serotonin antagonists (*e.g.* 5-HT₃ antagonists, 5-HT₄ antagonists *etc.*), darifenacin, polycarbophil calcium and so on.

The other pharmaceutical preparations to compensate and/or enhance for preventive and/or therapeutic effect on gastric ulcer and duodenal ulcer of the compounds in the present invention include, for example, peptic ulcer drugs (*e.g.* offensive factor inhibitors, antipeptic drugs, antacids, histamine-H₂ receptor antagonists, anti gastrin drugs, proton pump inhibitors, muscarine receptor inhibitors, anticholinergic drugs, defensive factor enhancers, prostaglandin derivatives, mesalazine, salazosulfapyridine, *etc.*), anticholinergic drugs, gastric mucosal paralytic drugs, antianxiety drugs (*e.g.* benzodiazepine anxiolytics, thienodiazepine anxiolytics, non-benzodiazepine anxiolytics, serotonergic drugs, CRF antagonists, *etc.*), dopamine antagonists and so on.

The other pharmaceutical preparations to compensate and/or enhance for preventive and/or therapeutic effect on ulcerative colitis of the compounds in the present invention include, for example, mesalazine, salazosulfapyridine, peptic ulcer drugs (*e.g.* offensive factor inhibitors, antipeptic drugs, antacids, histamine-H₂ receptor antagonists, anti gastrin drugs, proton pump inhibitors, muscarine receptor inhibitors, anticholinergic drugs, defensive factor enhancers, prostaglandin derivatives, *etc.*), anticholinergic drugs, steroids, 5-lipoxygenase inhibitors, antioxidant drugs, LTB₄ antagonists, local anesthetics, immunosuppressive drugs, defensive factor enhancers, metalloprotease inhibitors and so on.

The other pharmaceutical preparations to compensate and/or enhance for preventive and/or therapeutic effect on biliary tract dyskinesia of the compounds in the

present invention include, for example, ceruleins, antispasmodic drugs, COMT (catechol-O-methyltransferase) inhibitors, cholinergic agonists, anticholinergic drugs, antianxiety drugs, cholagogues, antidepressants, CCK-A antagonists and so on.

5 The other pharmaceutical preparations to compensate and/or enhance for preventive and/or therapeutic effect on aerophagy of the compounds in the present invention include, for example, intestinal remedies, antianxiety drugs, autonomic nerve modulators, fiber formulations, digestive enzymes, gas absorbent drugs, intestinal tract prokinetic drugs and so on.

10 The other pharmaceutical preparations to compensate and/or enhance for preventive and/or therapeutic effect on chronic hepatitis of the compounds in the present invention include, for example, liver hydrolysate formulations, polyenephosphatidylcholine, glycyrrhizin formulations, protoporphyrin sodium, ursodeoxycholic acid, steroids, anticholinergic drugs, antacids, propagermanium, lipid peroxidase inhibitors and so on.

15 The other pharmaceutical preparations to compensate and/or enhance for preventive and/or therapeutic effect on chronic pancreatitis of the compounds in the present invention include, for example, protease inhibitors, gastric acid inhibitors, antispasmodic drugs (*e.g.* COMT inhibitors, anti serotonin drugs *etc.*), nonsteroidal anti-inflammatory drugs, central analgesics, sedatives, digestive enzymes, antacids, 20 histamine H₂ receptor inhibitors, antidepressants, gastric mucosa local anesthetics, gastrointestinal tract function regulators (CCK-A antagonists) and so on.

The other pharmaceutical preparations to compensate and/or enhance for preventive and/or therapeutic effect on esophageal spasm of the compounds in the present invention include, for example, esophageal prokinetic drugs, antianxiety drugs, 25 autonomic nerve modulators and so on.

The other pharmaceutical preparations to compensate and/or enhance for preventive and/or therapeutic effect on gastric atony of the compounds in the present invention include, for example, gastrointestinal tract prokinetic drugs, digestive enzymes, tranquilizers and so on.

30 The other pharmaceutical preparations to compensate and/or enhance for preventive and/or therapeutic effect on functional dyspepsia of the compounds in the present invention include, for example, antacids, histamine H₂ receptor inhibitors, gastrointestinal tract function regulators, gastrointestinal tract prokinetic drugs, antianxiety drugs, tranquilizers, digestive enzymes, proton pump inhibitors, muscarine 35 receptor inhibitors, anticholinergic drugs, defensive factor enhancers, dopamine antagonists and so on.

Antianxiety drugs include, for example, diazepam, oxazolam, flunitrazepam, alprazolam, etizolam, flutazolam, lorazepam, ethyl loflazepate, tofisopam, clotiazepam, γ oryzanol and so on.

5 Tricyclic antidepressants include, for example, amitriptyline, imipramine, clomipramine, nortriptyline, desipramine, amoxapine and so on.

Tetracyclic antidepressants include, for example, mianserin, maprotiline and so on.

Monoamine oxidase inhibitors include, for example, trazodone, fluvoxamine and so on.

10 Antiparkinson drugs include, for example, levodopa, amantadine, selegiline, bromocriptine, pramipexole, anticholinergic drug and so on.

Anticholinergic drugs include, for example, trihexyphenidyl, biperiden, ipratropium bromide, mepenzolate bromide and so on.

15 Antiepileptic drugs include, for example, phenobarbital, phenytoin, carbamazepine, valproic acid, clonazepam and so on.

Anti vertigo drugs include, for example, difenidol, betahistine and so on.

Asthmatic drugs include, for example, ephedrine, orciprenaline, salbutamol, procaterol, theophylline, aminophylline, disodium cromoglycate, anticholinergic drug, inhaled steroid and so on.

20 Inhaled steroids include, for example, beclomethasone, prednisolone and so on.

Antipeptic drugs include, for example, sucralfate and so on.

Antacids include, for example, sodium hydrogen carbonate, magnesium oxide, dry aluminum hydroxide gel, aluminum silicate and so on.

25 Histamine H₂ receptor inhibitors include, for example, famotidine, ranitidine, cimetidine, roxatidine and so on.

Anti gastrin drugs include, for example, proglumide and so on.

Proton pump inhibitors include, for example, omeprazole, lansoprazole and so on.

30 Muscarine receptor inhibitors include, for example, pirenzepine and so on.

Defensive factor enhancers include, for example, gefarnate, teprenone, sucralfate, aldioxa, cetraxate hydrochloride, ornoprostil and so on.

Prostaglandin derivatives include, for example, ornoprostil, misoprostol and so on.

35 Gastrointestinal tract function regulators include, for example, cisapride, domperidone, sulpiride, metoclopramide, alosetron, trimebutine maleate and so on.

Gastrointestinal tract prokinetic drugs include, for example, cisapride, tegaserod, bethanechol hydrochloride and so on.

Antidiarrheals include, for example, loperamide and so on.

5 Bulk laxatives include, for example, methylcellulose, carmellose, lactulose and so on.

Saline laxatives include, for example, magnesium sulfate, magnesium oxide and so on.

Stimulant laxatives include, for example, picosulfate, lactulose, castor oil, senna, rhubarb and so on.

10 Antihypertensive drugs include, for example, nicardipine, nifedipine, nilvadipine, atenolol, allotynol, carteolol, propranolol, metoprolol, prazosin, captopril, enalapril, candesartan cilexetil, losartan potassium and so on.

Antiarrhythmic drugs include, for example, quinidine, procainamide, disopyramide, lidocaine, mexiletine, propranolol, amiodarone, verapamil and so on.

15 Cardiac stimulants include, for example, digitoxin, digoxin, dopamine, dobutamine, aminophylline, mirnoline and so on.

Dysuria remedies include, for example, oxybutynin, tamsulosin, propiverine and so on.

20 Local anesthetics include, for example, lidocaine, oxethazaine, procaine hydrochloride, dibucaine hydrochloride, cocaine hydrochloride, tetracaine hydrochloride and so on.

Immunosuppressive drugs include, for example, cyclosporine, tacrolimus, azathiopurine, FTY720 and so on.

Autonomic nerve modulators include, for example, γ orizanol and so on.

25 Cholagogues include, for example, ursodeoxycholic acid and so on.

Tachykinin NK1 antagonists include, for example, aprepitant and so on.

30 In order to use the compounds in the present invention, or the compounds in the present invention in combination with the other pharmaceutical preparations by the above-mentioned purpose, these compounds are normally administered to the entire of human body or topically, and orally or parenterally.

The dose of the compounds in the present invention depends on age, body weight, symptom, therapeutic effect, the administration method, the treatment time and so on. In practice, however, these compounds are administered orally once or several times per day each in an amount of from 100 μ g to 1000mg per adult, parentally once or
35 several times per day each in an amount of from 50 μ g to 500mg per adult or continuously administered into vein for 1 hour to 24 hours per day.

It goes without saying that the dose of these compounds may be less than the above-mentioned dose or may need to exceed the above-mentioned range because the dose varies under various conditions as mentioned above.

When the compounds in the present invention, or the compounds in the present invention are administered in combination with the other pharmaceutical preparations, they are used in the form of solid or liquid agent for oral administration, injection, agent for external application, suppository, eye drops or inhalant for parenteral administration or the like.

Examples of the solid agent for oral administration include tablet, pill, capsule, powder, and pellet. Examples of the capsule include hard capsule, and soft capsule.

In such a solid agent for internal application, one or more active materials are used in the form of preparation produced by an ordinary method singly or in admixture with a vehicle (*e.g.*, lactose, mannitol, glucose, microcrystalline cellulose, starch *etc.*), binder (*e.g.*, hydroxypropyl cellulose, polyvinyl pyrrolidone, magnesium metasilicoaluminate *etc.*), disintegrant (*e.g.*, calcium fibrinoglycolate *etc.*), glidant (*e.g.*, magnesium stearate *etc.*), stabilizer, dissolution aid (*e.g.*, glutamic acid, aspartic acid *etc.*) or the like. The solid agent may be coated with a coating agent (*e.g.*, white sugar, gelatin, hydroxypropyl cellulose, hydroxypropyl methyl cellulose phthalate *etc.*) or two or more layers. Alternatively, the solid agent may be capsulized by an absorbable material such as gelatin.

Examples of the liquid agent for oral administration include pharmaceutically acceptable aqueous solution, suspension, emulsion, syrup, and elixir. In such a liquid agent, one or more active agents are dissolved, suspended or emulsified in a commonly used diluent (*e.g.*, purified water, ethanol, mixture thereof *etc.*). Furthermore, such a liquid agent may comprise a wetting agent, a suspending agent, an emulsifier, a sweetening agent, a flavor, a fragrance, a preservative, a buffer, *etc.*

The agent for parenteral administration may be in the form of, *e.g.*, ointment, gel, cream, wet compress, paste, liniment, nebula, inhalant, spray, aerosol, eye drops, collunarium or the like. These agents each contain one or more active materials and are prepared by any known method or commonly used formulation.

The ointment is prepared by any known or commonly used formulation. For example, one or more active materials are triturated or dissolved in a base to prepare such an ointment. The ointment base is selected from known or commonly used materials. In some detail, higher aliphatic acid or higher aliphatic acid ester (*e.g.*, myristic acid, palmitic acid, stearic acid, oleic acid, myristic acid ester, palmitic acid

ester, stearic acid ester, oleic acid ester *etc.*), wax (*e.g.*, beeswax, whale wax, ceresin *etc.*), surface active agent (*e.g.*, polyoxyethylenealkylether phosphoric acid ester *etc.*), higher alcohol (*e.g.*, cetanol, stearyl alcohol, setostearyl alcohol *etc.*), silicon oil (*e.g.*, dimethyl polysiloxane *etc.*), hydrocarbon (*e.g.*, hydrophilic petrolatum, white petrolatum, purified lanolin, liquid paraffin *etc.*), glycol (*e.g.*, ethylene glycol, diethylene glycol, propylene glycol, polyethylene glycol, macrogol *etc.*), vegetable oil (*e.g.*, castor oil, olive oil, sesame oil, turpentine oil), animal oil (mink oil, vitelline oil, squalane, squalene), water, absorption accelerator and rash preventive may be used singly or in admixture of two or more thereof. The base may further comprise a humectant, a preservative, a stabilizer, an antioxidant, a perfume, *etc.*

The gel is prepared by any known or commonly used formulation. For example, one or more active materials are dissolved in a base to prepare such a gel. The gel base is selected from known or commonly used materials. For example, lower alcohol (*e.g.*, ethanol, isopropyl alcohol *etc.*), gelling agent (*e.g.*, carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, ethyl cellulose *etc.*), neutralizing agent (*e.g.*, triethanolamine, diisopropanolamine *etc.*), surface active agent (*e.g.*, polyethylene glycol monostearate *etc.*), gums, water, absorption accelerator, and rash preventive are used singly or in admixture of two or more thereof. The gel base may further comprise a preservative, an antioxidant, a perfume, *etc.*

The cream is prepared by any known or commonly used formulation. For example, one or more active materials are dissolved in a base to prepare such a cream. The cream base is selected from known or commonly used materials. For example, higher aliphatic acid ester, lower alcohol, hydrocarbon, polyvalent alcohol (*e.g.*, propylene glycol, 1,3-butylene glycol *etc.*), higher alcohol (*e.g.*, 2-hexyl decanol, cetanol *etc.*), emulsifier (*e.g.*, polyoxyethylene alkyl ethers, aliphatic acid esters *etc.*), water, absorption accelerator, and rash preventive are used singly or in admixture of two or more thereof. The cream base may further comprise a preservative, an antioxidant, a perfume, *etc.*

The wet compress is prepared by any known or commonly used formulation. For example, one or more active materials are dissolved in a base to prepare a kneaded mixture which is then spread over a support to prepare such a wet compress. The wet compress base is selected from known or commonly used materials. For example, thickening agent (*e.g.*, polyacrylic acid, polyvinyl pyrrolidone, gum arabic, starch, gelatin, methyl cellulose *etc.*), wetting agent (*e.g.*, urea, glycerin, propylene glycol *etc.*), filler (*e.g.*, kaolin, zinc oxide, talc, calcium, magnesium *etc.*), water, dissolution aid, tackifier, and rash preventive may be used singly or in admixture of two or more thereof.

The wet compress base may further comprise a preservative, an antioxidant, a perfume, *etc.*

The pasting agent is prepared by any known or commonly used formulation. For example, one or more active materials are dissolved in a base to prepare a kneaded mixture which is then spread over a support to prepare such a pasting agent. The pasting agent base is selected from known or commonly used materials. For example, polymer base, fat and oil, higher aliphatic acid, tackifier and rash preventive may be used singly or in admixture of two or more thereof. The pasting agent base may further comprise a preservative, an antioxidant, a perfume, *etc.*

The liniment is prepared by any known or commonly used formulation. For example, one or more active materials are dissolved, suspended or emulsified in water, alcohol (*e.g.*, ethanol, polyethylene glycol *etc.*), higher aliphatic acid, glycerin, soap, emulsifier, suspending agent, *etc.*, singly or in combination of two or more thereof, to prepare such a liniment. The liniment may further comprise a preservative, an antioxidant, a perfume, *etc.*

The nebula, inhalant, spray and aerosol each may comprise a commonly used diluent, additionally, a stabilizer such as sodium hydrogen sulfite and a buffer capable of providing isotonicity such as isotonic agent (*e.g.*, sodium chloride, sodium citrate, or citric acid *etc.*). For the process for the preparation of spray, reference can be made to US Patents 2,868,691 and 3,095,355.

The injection for parenteral administration consists of solid injection used to be dissolved or suspended in the form of solution, suspension, emulsion and a solvent to be dissolved before use. The injection is prepared by dissolving, suspending or emulsifying one or more active materials in a solvent. As such a solvent there may be used distilled water for injection, physiological saline, vegetable oil, alcohol such as propylene glycol, polyethylene glycol and ethanol, *etc.*, singly or in combination thereof. The injection may further comprise a stabilizer, a dissolution aid (*e.g.*, glutamic acid, aspartic acid, Polysolvate 80 (trade name) *etc.*), a suspending agent, an emulsifier, a soothing agent, a buffer, a preservative, *etc.* The injection is sterilized at the final step or prepared by an aseptic process. Alternatively, an aseptic solid agent such as freeze-dried product which has previously been prepared may be rendered aseptic or dissolved in aseptic distilled water for injection or other solvents before use.

The eye drops for parenteral administration consist of eye drop, suspension eye drop, emulsion eye drop, eye drop to be dissolved before use and ointment and so on.

These eye drops are prepared by a known method. For example, it is prepared by dissolving, suspending or emulsifying one or more active materials in a solvent. As such a solvent for eye drops there may be used sterile purified water, physiological saline, the other aqueous solvent or nonaqueous solvent for injection (e.g. vegetable oil *etc.*), *etc.*, singly or in combination thereof. The eye drops may comprise, if necessary, of materials properly selected from tonicity agent (e.g. sodium chloride, concentrated glycerin *etc.*), buffer agents (e.g. sodium phosphate, sodium acetate *etc.*), surfactants (e.g. polysorbate 80 (trade name), polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil *etc.*), stabilizer (e.g. sodium citrate, sodium edentate *etc.*), antiseptic agent (e.g. benzalkonium chloride, paraben *etc.*). These are sterilized at the final step or prepared by an aseptic process. Alternatively, an aseptic solid agent such as freeze-dried product which has previously been prepared may be rendered aseptic or dissolved in aseptic distilled water for injection or other solvents before use.

The inhalant for parenteral administration may be in the form of aerosol, powder for inhalation or liquid for inhalation. The liquid for inhalation may be dissolved or suspended in water or other proper medium in use.

These inhalants are prepared by a known method.

For example, the liquid for inhalation is prepared from materials properly selected from preservatives (e.g., benzalconium chloride, Paraben *etc.*), colorants, buffering agents (e.g., sodium phosphate, sodium acetate *etc.*), isotonic agents (e.g., sodium chloride, concentrated glycerin *etc.*), thickening agents (e.g., carboxyvinyl polymer *etc.*), absorption accelerators, *etc.* as necessary.

The powder for inhalation is prepared from materials properly selected from glidants (e.g., stearic acid and salt thereof *etc.*), binders (e.g., starch, dextrin *etc.*), vehicles (e.g., lactose, cellulose *etc.*), colorants, preservatives (e.g., benzalconium chloride, Paraben *etc.*), absorption accelerators, *etc.*, if necessary.

In order to administer the liquid for inhalation, a sprayer (e.g., atomizer, nebulizer *etc.*) is normally used. In order to administer the powder for inhalation, a powder inhaler is normally used.

Other examples of the composition for parenteral administration include suppository for rectal administration and pessary for vaginal administration prepared by an ordinary formulation comprising one or more active materials.

Best Mode for Carrying Out the Invention

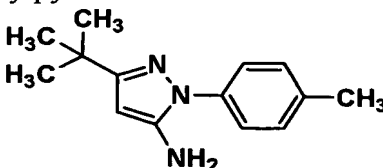
The present invention is explained below in detail base on Examples, however, the present invention is not limited thereto. The solvents in parentheses at

chromatographic separations section and TLC section show the developing or eluting solvents and the ratios of the solvents used are indicated by volume. NMR is the measurement of ^1H NMR. The solvents in parentheses indicated in NMR section show solvents used in determination, unless noting deuterated chloroform used as the solvent.

All compounds described in the specification are named by using of ACD/Name (Trade mark, Advanced Chemistry Development Inc.) or ACD/Name batch (Trade mark, Advanced Chemistry Development Inc.) which is the computer program to name according to IUPAC rule, or according to IUPAC organic chemistry nomenclature.

Example 1

1-(4-methylphenyl)-3-*tert*-butylpyrazol-5-amine:



A solution of 4-methylphenylhydrazine (0.90mL) and 4,4-dimethyl-3-oxopentanenitrile (1.0g) in toluene (3mL) was refluxed overnight. The reaction mixture was concentrated and the residue was purified by column to give the title compound (1.53g).

Example 1(1) - Example 1(9)

By the same procedure as described method showed in Example 1 (the method described in "*J. Med. Chem.*, 45, 2994-3008 (2002)") using 4-methylphenylhydrazine, or *tert*-butylhydrazine or 4-(chlorophenyl)hydrazine instead thereof and 4-oxotetrahydro-3-thiophenecarbonitrile, 2-amino-1-cyclopentane-1-carbonitrile, 2-amino-1-cycloheptane-1-carbonitrile, 3-oxo-2-phenylpropanenitrile, 2-oxocyclohexanecarbonitrile or 1-*tert*-butoxycarbonyl-4-oxo-3-pyrrolidinecarbonitrile instead of 4,4-dimethyl-3-oxopentanenitrile, the following compounds were obtained.

Example 1(1)

2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-amine:

TLC: Rf 0.32 (n-hexane : ethyl acetate = 2 : 1);

NMR: δ 1.62 (s, 9H), 3.43 (s, 2H), 3.73 (m, 2H), 3.93 (m, 2H).

Example 1(2)

2-(4-chlorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-amine:

TLC: R_f 0.33 (n-hexane : ethyl acetate = 2 : 1);

NMR: δ 3.69 (s, 2H), 3.79 (t, J=1.19 Hz, 2H), 3.97 (t, J=1.28 Hz, 2H), 7.47 (m, 4H).

5

Example 1(3)

2-(4-methylphenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-amine:

TLC: R_f 0.26 (n-hexane : ethyl acetate = 2 : 1);

NMR: δ 2.40 (s, 3H), 3.69 (s, 2H), 3.80 (t, J=1.37 Hz, 2H), 3.98 (t, J=1.37 Hz, 2H), 7.27 (m, 2H), 7.39 (m, 2H).

10

Example 1(4)

2-(4-chlorophenyl)-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-amine:

TLC: R_f 0.53 (hexane : ethyl acetate = 2 : 1);

NMR: δ 2.40 (m, 2H), 2.56 (m, 2H), 2.70 (m, 2H), 3.63 (s, 2H), 7.41 (m, 2H), 7.53 (m, 2H).

15

Example 1(5)

2-*tert*-butyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-amine:

TLC: R_f 0.38 (n-hexane : ethyl acetate = 2 : 1);

NMR: δ 1.63 (s, 9H), 2.33 (m, 2H), 2.47 (m, 2H), 2.64 (t, J=7.23 Hz, 2H), 3.40 (s, 2H).

20

Example 1(6)

2-(4-chlorophenyl)-2,4,5,6,7,8-hexacyclohepta[c]pyrazol-3-amine:

TLC: R_f 0.45 (n-hexane : ethyl acetate = 2 : 1);

NMR: δ 1.70 (m, 4H), 1.84 (m, 2H), 2.37 (m, 2H), 2.71 (m, 2H), 3.48 (s, 2H), 7.40 (m, 2H), 7.53 (m, 2H).

25

Example 1(7)

1-*tert*-butyl-4-phenyl-1H-pyrazol-5-amine:

TLC: R_f 0.42 (n-hexane : ethyl acetate = 2 : 1);

NMR: δ 1.70 (s, 9H), 3.79 (s, 2H), 7.21 (m, 2H), 7.39 (m, 4H).

30

Example 1(8)

2-(4-chlorophenyl)-4,5,6,7-tetrahydro-2H-indazol-3-amine:

TLC: R_f 0.33 (n-hexane : ethyl acetate = 3 : 1);

35

NMR: δ 1.80 (m, 4H), 2.37 (t, $J=5.77$ Hz, 2H), 2.65 (t, $J=5.95$ Hz, 2H), 3.56 (s, 2H), 7.41 (m, 2H), 7.53 (m, 2H).

Example 1(9)

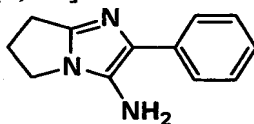
5 *tert*-butyl 3-amino-2-(4-chlorophenyl)-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4H)-carboxylate:

TLC: R_f 0.54 (ethyl acetate : *n*-hexane = 1 : 1);

NMR: δ 1.51 (s, 9H), 3.60-4.00 (b, 2H), 4.34-4.43 (m, 4H), 7.42-7.54 (m, 4H).

10 Example 2:

2-phenyl-6,7-dihydro-5H-pyrrolo[1,2-*a*]imidazol-3-amine:



A solution of 2-pyrrolidinone (0.76mL) in toluene (5mL) was added by phosphoryl chloride (0.47mL) under the ice and the mixture was stirred for 3 hours.

15 The mixture was added by amino(phenyl)acetonitrile hydrochloride (843mg) and the mixture was stirred overnight at room temperature. The upper layer of the mixture was removed and additionally washed with toluene. The lower layer was added by 2N aqueous sodium hydroxide solution (ca. 20mL) and extracted by toluene. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then
20 concentrated to give the compound of the present invention (431mg) having the following physical data.

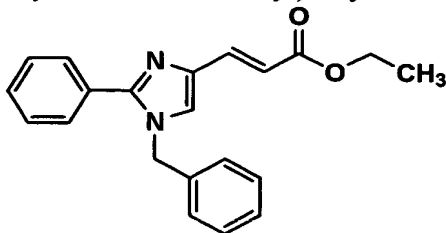
TLC: R_f 0.45 (methylene chloride : methanol : 28% ammonia water = 9 : 1 : 0.1);

NMR: δ 2.60 (m, 2H), 2.88 (m, 2H), 3.34 (s, 2H), 3.86 (m, 2H), 7.16 (m, 1H), 7.37 (m, 2H), 7.69 (m, 2H).

25

Example 3

ethyl(2E)-3-(1-benzyl-2-phenyl-1H-imidazol-4-yl)acrylate:



30 A solution of 4-formyl-2-phenylimidazole (8.68g) in dimethylformamide (100mL) was added by potassium carbonate (10.5g), benzylbromide (6.0mL) and the

mixture was stirred for 2.5 hours at room temperature. The reaction mixture was added by water and extracted by ethyl acetate. The organic layer was washed with saturated brine, dried and then concentrated to give 1-benzyl-4-formyl-2-phenylimidazole (14.7g).

After that, a suspension of sodium hydride (62.7% in oil, 2.30g) in tetrahydrofuran (100mL) was dropped by ethyl(diethoxyphosphoryl)acetate (12mL) under the ice and stirred for 10 minutes. This reaction solution was dropped by the above described solution of 1-benzyl-4-formyl-2-phenylimidazole (14.7g) in tetrahydrofuran (100mL) for 20 minutes and stirred for 2 hours at room temperature.

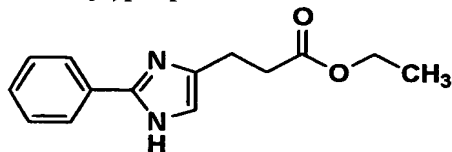
The reaction mixture was added by water and extracted by ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and then concentrated. The residue was recrystallized from mixed solvent (n-hexane : ethyl acetate = 2 : 1) to give the compound of the present invention (5.26g) having the following physical data.

TLC: R_f 0.37 (n-hexane : ethyl acetate = 2 : 1);

NMR: δ 1.30 (t, J=7.14 Hz, 3H), 4.23 (q, J=7.08 Hz, 2H), 5.18 (s, 2H), 6.64 (d, J=15.56 Hz, 1H), 7.09 (m, 2H), 7.14 (s, 1H), 7.37 (m, 6H), 7.56 (m, 3H).

Example 4

ethyl 3-(2-phenyl-1H-imidazol-4-yl)propanoate:



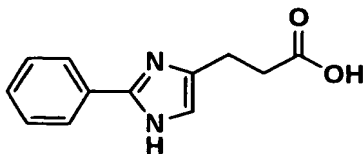
Under atmosphere of argon, a solution of the compound (5.22g) prepared in Example 3 in ethanol (160mL) was added by 10% palladium carbon (1.62g) and the mixture was stirred for 9 hours at 50 °C under atmosphere of hydrogen. The reaction mixture was filtrated after standing to cool and the filtrate was concentrated to give the compound of the present invention (3.79g) having the following physical data.

TLC: R_f 0.37 (n-hexane : ethyl acetate = 2 : 1);

NMR (DMSO- d_6): δ 1.17 (t, J=7.05 Hz, 3H), 2.72 (m, 4H), 4.06 (q, J = 7.14 Hz, 2H), 6.84 (m, 1H), 7.34 (m, 3H), 7.87 (m, 2H), 12.23 (s, 1H).

Example 5

3-(2-phenyl-1H-imidazol-4-yl)propanoic acid:



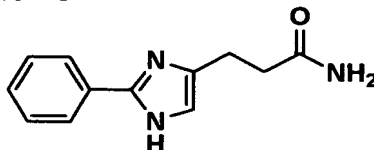
A solution of the compound (3.76g) prepared in Example 4 in ethanol (30mL) was added by 2N aqueous sodium hydroxide solution (16mL) and the mixture was stirred overnight at room temperature. The reaction mixture was dropped by 2N hydrochloric acid (16mL) under the ice and stirred at 0 °C. The precipitate was filtrated and then washed with water to give the compound (3.23g) of the present invention having the following physical data.

TLC: Rf 0.14 (ethyl acetate : methanol = 9 : 1);

NMR (DMSO-d₆): δ 2.57 (t, J=7.41 Hz, 2H), 2.77 (t, J=7.51 Hz, 2H), 6.86 (s, 1H), 7.29 (m, 1H), 7.40 (m, 2H), 7.87 (m, 2H), 12.23 (s, 1H).

Example 6

3-(2-phenyl-1H-imidazol-4-yl)propanamide:



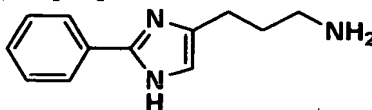
A suspension of the compound (2.16g) prepared in Example 5 in dioxane (18mL) was added by 28% aqueous ammonia solution (54mL) under the ice and the mixture was stirred for 1 day at room temperature. The reaction mixture was extracted by ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and then concentrated. The residue was recrystallized from mixed solvent (n-hexane : ethyl acetate = 1 : 2) to give the compound of the present invention (1.34g) having the following physical data.

TLC: Rf 0.26 (ethyl acetate : methanol = 9 : 1);

NMR (DMSO-d₆): δ 2.40 (m, 2H), 2.76 (m, 2H), 6.78 (m, 2H), 7.33 (m, 4H), 7.87 (m, 2H), 12.18 (s, 1H).

Example 7

3-(2-phenyl-1H-imidazol-4-yl)-1-propanamine:



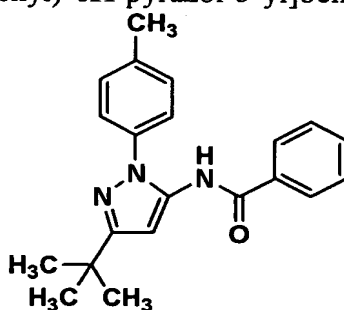
A solution of lithium aluminum hydride (1.42g) in dioxane (50mL) was gradually added by the compound (1.09g) prepared in Example 6 under reflux and the

mixture was stirred for 2 hours. The reaction mixture was dropped by 2N aqueous sodium hydroxide solution (7.1mL) under the ice after standing to cool and the mixture was stirred for 1 hour at 0°C. The mixture was added by adequate amount of sodium sulfate, filtrated and then the filtrate was concentrated to give the compound of the present invention (1.11g) having the following physical data.

TLC: R_f 0.31 (methylene chloride : methanol : 28% ammonia water = 9 : 1 : 0.1);
NMR: δ 1.80 (m, 2H), 2.74 (m, 2H), 2.84 (t, J=6.41 Hz, 2H), 6.82 (t, J=0.82 Hz, 1H), 7.32 (m, 3H), 7.82 (m, 2H).

10 Example 8

N-[3-*tert*-butyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]benzamide:



A solution of the compound (115mg) prepared in Example 1 in pyridine (1mL) was added by benzoyl chloride (84mg) at room temperature and the mixture was stirred overnight. The reaction mixture was concentrated and the residue was added by water, extracted by ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine successively, dried over anhydrous sodium sulfate and then concentrated. The residue was recrystallized from mixed solvent of hexane and ethyl acetate to give the compound of the present invention (60mg) having the following physical data.

TLC: R_f 0.39 (ethyl acetate : hexane = 1 : 3);
NMR: δ 1.38 (d, J=2.20 Hz, 9H), 2.42 (s, 3H), 6.78 (s, 1H), 7.33 (d, J=8.06 Hz, 2H), 7.43 (m, 4H), 7.54 (m, 1H), 7.72 (m, 2H), 7.98 (s, 1H).

25 Example 8(1) - Example 8(16)

By the same procedure as described in Example 8 using the compound prepared in Example 1, or the compound prepared in Example 1(1) - 1(9) or the compound prepared in Example 7 instead thereof and benzochloride or halide compound instead thereof, the following compounds of the present invention were obtained.

Example 8(1)

N-[3-*tert*-butyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-(4-fluorophenyl)acetamide:

TLC: R_f 0.28 (ethyl acetate : hexane = 1 : 3);

5 NMR: δ 1.32 (s, 9H), 2.38 (s, 3H), 3.65 (s, 2H), 6.60 (s, 1H), 6.98 (m, 4H), 7.12 (m, 5H).

Example 8(2)

N-[3-*tert*-butyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide:

TLC: R_f 0.33 (ethyl acetate : hexane = 1 : 3);

10 NMR: δ 1.37 (s, 9H), 2.42 (s, 3H), 6.71 (s, 1H), 7.08 (dd, J=4.94, 3.84 Hz, 1H), 7.33 (m, J=8.60 Hz, 2H), 7.40 (m, 3H), 7.54 (dd, J=4.94, 1.10 Hz, 1H), 7.81 (s, 1H).

Example 8(3)

N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)benzamide:

15 TLC: R_f 0.39 (n-hexane : ethyl acetate = 2 : 1);

NMR (DMSO-*d*₆): δ 1.54 (s, 9H), 3.66 (s, 2H), 3.90 (s, 2H), 7.59 (m, 3H), 7.94 (m, 2H), 10.02 (s, 1H).

Example 8(4)

20 N-[2-(4-chlorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-2-phenylacetamide:

TLC: R_f 0.53 (ethyl acetate : hexane = 1 : 1);

NMR: δ 3.69 (s, 2H), 3.97 (s, 2H), 4.05 (s, 2H), 6.96 (s, 1H), 7.05 (m, 2H), 7.26 (m, 7H).

Example 8(5)

25 N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)-2-(4-fluorophenyl)acetamide:

TLC: R_f 0.44 (ethyl acetate : hexane = 1 : 1);

NMR (DMSO-*d*₆): δ 1.42 (s, 9H), 3.56 (s, 2H), 3.63 (s, 2H), 3.84 (s, 2H), 7.15 (m, 2H), 7.33 (m, 2H), 9.68 (s, 1H).

30

Example 8(6)

N-(1-*tert*-butyl-4-phenyl-1H-pyrazol-5-yl)-2-(4-fluorophenyl)acetamide:

TLC: R_f 0.39 (ethyl acetate : hexane = 2 : 3);

NMR (DMSO-*d*₆): δ 1.48 (s, 9H), 3.63 (s, 2H), 7.19 (m, 5H), 7.33 (m, 4H), 7.69 (s, 1H),

35

9.91 (s, 1H).

Example 8(7)

N-(1-*tert*-butyl-4-phenyl-1H-pyrazol-5-yl)-3-phenylpropanamide:

TLC: R_f 0.45 (ethyl acetate : hexane = 2 : 3);

5 NMR (DMSO-*d*₆): δ 1.47 (s, 9H), 2.64 (t, J=7.60 Hz, 2H), 2.88 (t, J=7.51 Hz, 2H), 7.29 (m, 10H), 7.68 (s, 1H), 9.70 (s, 1H).

Example 8(8)

N-[2-(4-chlorophenyl)-2,6-dihydro-4H-thieno[3,4-*c*]pyrazol-3-yl]-3-phenylpropanamide:

10 TLC: R_f 0.50 (ethyl acetate : hexane = 2 : 3);

NMR (DMSO-*d*₆): δ 2.57 (t, J=7.41 Hz, 2H), 2.85 (t, J=7.23 Hz, 2H), 3.71 (s, 2H), 3.94 (s, 2H), 7.22 (m, 5H), 7.35 (m, 2H), 7.47 (m, 2H), 10.00 (s, 1H).

Example 8(9)

15 N-[3-(2-phenyl-1H-imidazol-4-yl)propyl]benzamide:

TLC: R_f 0.28 (n-hexane : ethyl acetate = 1 : 9);

NMR (DMSO-*d*₆): δ 1.86 (m, 2H), 2.60 (m, 2H), 3.33 (m, 2H), 6.91 (m, 1H), 7.40 (m, 6H), 7.85 (m, 4H), 8.50 (q, J=5.55 Hz, 1H), 12.19 (s, 1H).

20 Example 8(10)

2,5-dichloro-N-[3-(2-phenyl-1H-imidazol-4-yl)propyl]benzamide:

TLC: R_f 0.42 (n-hexane : ethyl acetate = 1 : 3);

25 NMR (DMSO-*d*₆): δ 1.84 (m, 2H), 2.60 (m, 2H), 3.29 (m, 2H), 6.88 (s, 1H), 7.29 (t, J=7.32 Hz, 1H), 7.40 (t, J=7.60 Hz, 2H), 7.51 (m, 3H), 7.87 (d, J=7.32 Hz, 2H), 8.60 (t, J=5.40 Hz, 1H), 12.19 (s, 1H).

Example 8(11)

N-[2-(4-chlorophenyl)-4,5,6,7-tetrahydro-2H-indazol-3-yl]-2-(4-fluorophenyl)acetamide:

30 TLC: R_f 0.40 (ethyl acetate : hexane = 2 : 3);

NMR (DMSO-*d*₆): δ 1.70 (m, 4H), 2.27 (t, J=5.95 Hz, 2H), 2.57 (t, J=6.04 Hz, 2H), 3.56 (s, 2H), 7.14 (m, 2H), 7.26 (m, 2H), 7.38 (m, 4H), 9.94 (s, 1H).

Example 8(12)

35 N-[2-(4-methylphenyl)-2,6-dihydro-4H-thieno[3,4-*c*]pyrazol-3-yl]-2-phenylacetamide:

TLC: R_f 0.32 (ethyl acetate : hexane = 1 : 2);

NMR: δ 2.39 (s, 3H), 3.66 (s, 2H), 3.98 (s, 2H), 4.09 (s, 2H), 7.04 (m, 5H), 7.17 (m, 2H), 7.30 (m, 3H).

Example 8(13)

5 N-[2-(4-chlorophenyl)-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl]-2-phenylacetamide:

TLC: R_f 0.35 (ethyl acetate : hexane = 2 : 3);

NMR: δ 2.38 (m, 2H), 2.72 (t, J=7.41 Hz, 2H), 2.81 (t, J=7.14 Hz, 2H), 3.68 (s, 2H), 6.96 (s, 1H), 7.06 (m, J=8.60 Hz, 2H), 7.24 (m, 4H), 7.34 (m, 3H).

10

Example 8(14)

N-(2-*tert*-butyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-2-phenylacetamide:

TLC: R_f 0.26 (ethyl acetate : hexane = 2 : 3);

15 NMR (DMSO- d_6): δ 1.40 (s, 9H), 2.24 (m, 2H), 2.33 (m, J=6.96, 6.96 Hz, 2H), 2.50 (m, 2H), 3.61 (s, 2H), 7.28 (m, 5H), 9.50 (s, 1H).

Example 8(15)

N-[2-(4-chlorophenyl)-2,4,5,6,7,8-hexahydrocyclohepta[c]pyrazol-3-yl]-2-phenylacetamide:

20 TLC: R_f 0.26 (ethyl acetate : hexane = 1 : 2);

NMR (DMSO- d_6): δ 1.57 (m, 4H), 1.79 (m, 2H), 2.29 (m, 2H), 2.67 (m, 2H), 3.57 (s, 2H), 7.28 (m, 9H), 9.91 (s, 1H).

Example 8(16)

25 *tert*-butyl 2-(4-chlorophenyl)-3-[[4-(4-fluorophenyl)acetyl]amino]-2,6-dihydropyrrolo[3,4-c]pyrazol-5(4H)-carboxylate:

TLC: R_f 0.49 (methylene chloride : ethyl acetate = 4 : 1);

NMR: δ 1.50 (d, J=4.03 Hz, 9H), 3.65 (d, J=6.77 Hz, 2H), 4.42 (d, J=14.65 Hz, 2H), 4.55 (d, J=14.83 Hz, 2H), 7.06 (m, 4H), 7.18 (m, 2H), 7.29 (m, 2H), 7.55 (s, 1H).

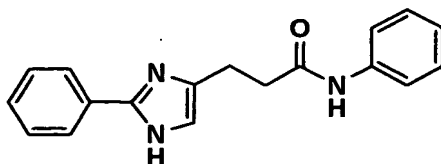
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Example 9 - Example 9(1)

By the same procedure as described in Example 8 using aniline or 3,5-dimethylaniline instead of the compound prepared in Example 1 and 3-(2-phenyl-1H-imidazol-4-yl)propanoylchloride instead of benzoylchloride, the following compounds
35 of the present invention were obtained.

Example 9

N-phenyl-3-(2-phenyl-1H-imidazol-4-yl)propanamide:



TLC: R_f 0.23 (n-hexane : ethyl acetate = 1 : 3);

5 NMR (DMSO-d₆): δ 2.67 (m, 2H), 2.88 (m, 2H), 6.97 (m, 2H), 7.29 (m, 3H), 7.41 (m, 2H), 7.59 (m, 2H), 7.88 (m, 2H), 9.96 (s, 1H), 12.24 (m, 1H).

Example 9(1)

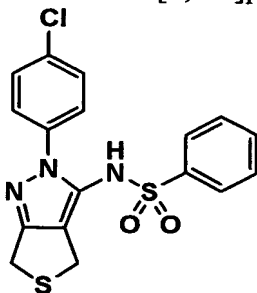
N-(3,5-dimethylphenyl)-3-(2-phenyl-1H-imidazol-4-yl)propanamide:

10 TLC: R_f 0.24 (n-hexane : ethyl acetate = 1 : 3);

NMR (DMSO-d₆): δ 2.21 (s, 6H), 2.64 (m, 2H), 2.86 (m, 2H), 6.65 (s, 1H), 6.85 (m, 1H), 7.21 (s, 2H), 7.29 (m, 1H), 7.41 (m, 2H), 7.87 (d, J=7.51 Hz, 2H), 9.81 (s, 1H), 12.22 (m, 1H).

15 Example 10

N-[2-(4-chlorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]benzenesulfonamide:



20 A solution of the compound (126mg) prepared in Example 1(2) in pyridine (1mL) was added by benzenesulfonylchloride (106mg) at room temperature and was stirred overnight. The reaction mixture was concentrated and the residue was added by water, extracted by ethyl acetate. The organic layer was washed with 1N hydrochloric acid, saturated aqueous sodium hydrogen carbonate solution and saturated brine successively, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = from 3 :
25 1 to 4 : 1), recrystallized and then recrystallized from mixed solvent of hexane/ethyl acetate to give the compound (55mg) having the following physical data.

TLC: R_f 0.34 (ethyl acetate : hexane = 1 : 2);

NMR (DMSO-d₆): δ 3.16 (s, 2H), 3.90 (s, 2H), 7.45 (m, 6H), 7.62 (m, 3H), 10.53 (s, 1H).

Example 10(1) - Example 10(4)

By the same procedure as described in Example 10 using the compound prepared in Example 1(2), or the compound prepared in Example 1(1) or Example 1(8) and benzenesulfonylchloride or benzylsulfonylchloride instead thereof, the following compounds of the present invention were obtained.

Example 10(1)

N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)benzenesulfonamide:

10 TLC: R_f 0.40 (n-hexane : ethyl acetate = 2 : 1);

NMR (DMSO-*d*₆): δ 1.55 (s, 9H), 2.69 (s, 2H), 3.75 (s, 2H), 7.68 (m, 3H), 7.82 (m, 2H), 10.09 (s, 1H).

Example 10(2)

15 N-[2-(4-chlorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-1-phenylmethanesulfonamide:

TLC: R_f 0.26 (ethyl acetate : hexane = 1 : 2);

NMR: δ 3.93 (m, 2H), 4.00 (m, 2H), 4.21 (s, 2H), 6.18 (m, 1H), 7.20 (m, 2H), 7.37 (m, 7H).

20

Example 10(3)

N-[2-(4-chlorophenyl)-4,5,6,7-tetrahydro-2H-indazol-3-yl]-1-phenylmethanesulfonamide:

TLC: R_f 0.26 (ethyl acetate : hexane = 1 : 2);

25 NMR: δ 1.83 (m, 4H), 2.60 (t, J=6.04 Hz, 2H), 2.71 (t, J=6.22 Hz, 2H), 4.08 (s, 2H), 6.09 (s, 1H), 7.24 (m, 2H), 7.33 (m, 3H), 7.43 (m, 4H).

Example 10(4)

30 N-[2-(4-chlorophenyl)-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl]-N-(phenylsulfonyl)benzenesulfonamide:

TLC: R_f 0.40 (n-hexane : ethyl acetate = 2 : 1);

NMR: δ 3.02 (m, 2H), 4.01 (m, 2H), 7.21 (m, 2H), 7.47 (m, 6H), 7.69 (m, 2H), 7.82 (m, 4H).

Example 11 - Example 11(1)

By the same procedure as described in Example 8 using the compound prepared in Example 2 instead of the compound prepared in Example 1 and phenylacetylchloride or (4-fluorophenyl)acetylchloride instead of benzoylchloride, the following compounds of the present invention were obtained.

Example 11

2-phenyl-N-(2-phenyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)acetamide:

TLC: R_f 0.45 (methanol : methylene chloride = 1 : 19);

NMR (DMSO-d₆): δ 2.49 (m, 2H), 2.77 (m, 2H), 3.71 (m, 4H), 7.14 (m, 1H), 7.23 (d, J=7.51 Hz, 7H), 7.63 (s, 2H), 9.58 (m, 1H).

Example 11(1)

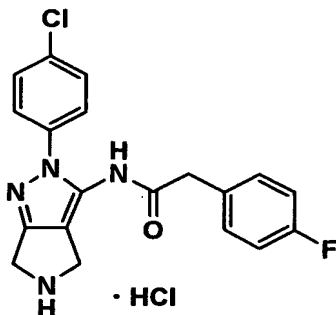
2-(4-fluorophenyl)-N-(2-phenyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)acetamide:

TLC: R_f 0.24 (ethyl acetate);

NMR (DMSO-d₆): δ 2.47 (m, 2H), 2.75 (t, J=7.51 Hz, 2H), 3.66 (s, 2H), 3.71 (t, J=6.96 Hz, 2H), 7.20 (m, 5H), 7.39 (m, 2H), 7.60 (m, 2H), 10.01 (s, 1H).

Example 12

N-[2-(4-chlorophenyl)-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-yl]-2-(4-fluorophenyl)acetamide hydrochloride:



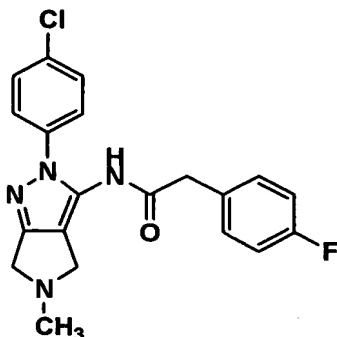
The compound prepared in Example 8(16) was added by 4N hydrogen chloride-dioxane solution and stirred. The reaction mixture was concentrated to give the following compound of the present invention.

TLC: R_f 0.40 (methanol : methylene chloride = 1 : 9);

NMR (DMSO-d₆): δ 3.65 (s, 2H), 4.30 (m, 4H), 7.16 (m, 2H), 7.29 (m, 2H), 7.48 (m, 2H), 7.58 (m, 2H), 9.91 (m, 2H), 10.55 (s, 1H).

Example 13

N-[2-(4-chlorophenyl)-5-methyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-yl]-2-(4-fluorophenyl)acetamide:

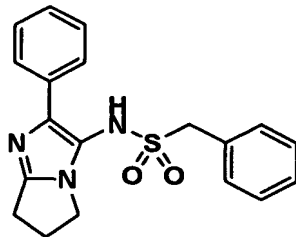


5 A solution of the compound prepared in Example 12 (31.4mg) in formic acid (0.5mL) was added by 37% aqueous formaldehyde solution (7μL) and the mixture was stirred for 5 hours at 100 °C. The reaction mixture was added by water, 1N hydrochloric acid and t-butylmethylether. The aqueous layer was added by 1N aqueous sodium hydroxide solution to control pH 8 and then extracted by methylene
10 chloride. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by column chromatography on silica gel (from methylene chloride : methanol = 19 : 1 to methylene chloride : methanol : 28% ammonia water = 10 : 2: 0.1) to give the compound of the present invention (22.6mg) having the following physical data.

15 TLC: R_f 0.53 (methanol : methylene chloride = 1 : 9);
NMR: δ 2.62 (s, 3H), 3.64 (s, 2H), 3.76 (s, 2H), 3.94 (s, 2H), 7.07 (m, 4H), 7.18 (m, 2H), 7.30 (m, 3H).

Example 14

20 1-phenyl-N-(2-phenyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)methanesulfonamide:



By the same procedure as described in Example 10 using the compound prepared in Example 2 instead of the compound prepared in Example 1(2) and

phenylmethanesulfonylchloride instead of benzenesulfonylchloride, the compound of the present invention having the following physical data was obtained.

TLC: R_f 0.50 (methanol : ethyl acetate = 1 : 19);

NMR: δ 2.56 (m, 2 H), 2.93 (t, J=7.51 Hz, 2 H), 3.97 (s, 2 H), 4.03 (t, J=7.32 Hz, 2 H),

5 7.14 (dd, J=7.60, 1.74 Hz, 2 H), 7.31 (m, 6 H), 7.76 (m, 2 H).

Biological Example 1

Receptor binding experiment:

The affinity of the compounds in the present invention to MBR was
10 determined using rat brain membrane preparation. In addition, the measurement in the present invention was improved the accuracy of measurement and the sensitivity of measurement for evaluating the compounds in the present invention as follows. After male Wister rats were decapitated to extirpate the whole brain and cerebellums were removed. They were homogenized in ice-cold 50mmol/L Tris-HCL buffer solution
15 (pH7.4), centrifuged and the obtained pellets were washed. The pellets resuspended and adjusted to about 1mg/mL were used as rat brain membrane preparations for binding assay. The binding assay were experimented using [³H]PK11195 as a MBR selective ligand. In addition, PK11195 was described in "European Journal of Pharmacology, 119, 153-167, 1985" as a MBR selective ligand, (1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isoquinolinecarboxamide).
20

To determine the amount of total binding in saturation binding experiment, membrane preparations, various concentrations of [³H]PK11195, final concentration: 0.5vol% dimethylsulfoxide (DMSO) and 50mmol/L Tris-HCL buffer solution (pH7.4) were mixed (total volume 200 μ L) and were incubated for 1 hour at room temperature.
25 To determine the amount of non-specific binding, the mixture was added by final concentration 20 μ mol/L of [³H]PK11195 instead of DMSO to be incubated for 1 hour. The mixture was rapidly filtrated on GF/B filter pretreated with 0.3% polyethyleneimine using cell harvester and washed over 50mmol/L Tris-HCL buffer solution (pH7.4) twice. The filter was dried and then the radioactivity on the filter was
30 measured by liquid scintillation counter. The data obtained by the binding experiments were Scatchard analyzed using analysis software, KELL (Ver.6, BIOSOFT) and the dissociation constant (K_D value) was determined.

To determine the amount of total binding in competition binding experiment, membrane preparations, final concentration 0.5 or 1nmol/L [³H]PK11195, final
35 concentration: 0.5vol% dimethylsulfoxide (DMSO) and 50mmol/L Tris-HCL buffer solution (pH7.4) were mixed (total volume 200 μ L) and were incubated for 1 hour at

room temperature. To determine the amount of non-specific binding, the mixture was added by final concentration 20 μ mol/L of PK11195 instead of DMSO to be incubated. In addition, to determine the affinity of the compounds in the present invention, the mixture was added by final concentration 10pmol/L to 1 μ mol/L of the solution of the compounds in the present invention in DMSO instead of DMSO to be incubated. After 1 hour, the mixture was saction filtrated by the above-mentioned method and the radioactivity on the filter was measured by liquid scintillation counter. The concentration of the compounds in the present invention (IC₅₀) which was necessary for inhibiting the amount of specific binding of [³H]PK11195 by 50% was determined from the obtained data. The inhibition constant (K_i value) was calculated according to Cheng and Prusoff formula (*Biochemical Pharmacology*, 22, 3099-3108 (1973)) using K_D value and IC₅₀.

In consequence, it was clear that the compounds in the present invention had high affinity to MBR.

For example, K_i value of the compound of Example 8(8) was 99nM.

Preparation Example 1:

The following components were admixed in conventional method, punched out to give 10000 tablets each containing 10mg of active ingredient.

N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)-2-(4-fluorophenyl)acetamide (100g)

carboxymethylcellulosecalcium (disintegrant) (20.0g)

magnesium stearate (lubricant) (10.0g)

microcrystalline cellulose (870g)

Preparation Example 2:

After mixing the following components by a conventional method, the resulting solution was filtrated by dust-proof filter and 5mL portions thereof were filled in amples, respectively, and heat-sterilized by autoclave to obtain 10000 amples of injection containing each 20mg of the active ingredient.

N-(2-*tert*-butyl-2,6-dihydro-4H-thieno[3,4-c]pyrazol-3-yl)-2-(4-fluorophenyl)acetamide (200g)

mannitol (2kg)

distilled water (50L)

Industrial Applicability

Since the compounds of the present invention represented by formula (I) have the affinity to MBR, they are useful for the prevention and/or treatment for disease induced or exacerbated and/or reignited by stressor or useful for the prevention and/or treatment for disease caused by stress.

The disease induced or exacerbated and/or reignited by stressor or the disease caused by stress include, for example, central nervous system diseases caused by stress (*e.g.* anxiety related disease (neurosis, psychosomatic disorder, generalized anxiety disorder (GAD), social-anxiety disorder (SAD), panic disorder, hyperactivity disorder, attention-deficit, personality disorder, bipolar disorder, autism *etc.*), sleep disorder, depression, reactive depression, epilepsy, Parkinson's disease, Perkinsonian syndrome, schizophrenia, autonomic dystonia, Huntington's disease, Alzheimer's disease, affective disorder, cognitive disorder, migraine, tension headache, cluster headache, posttraumatic stress disorder, dissociative disorder, insomnia, nervous vomiting, nervous cough, psychogenic convulsive seizure, psychogenic syncopal attack, maladjustment to job, burn-out syndrome, chronic fatigue syndrome, writer's cramp, spastic torticollis, *etc.*), respiratory system diseases caused by stress (*e.g.* asthma, bronchial asthma, hyperventilation syndrome, laryngeal spasm, chronic obstructive pulmonary diseases, *etc.*), digestive system diseases caused by stress (*e.g.* irritable bowel syndrome, peptic ulcer, functional dyspepsia, gastric ulcer, duodenal ulcer, ulcerative colitis, biliary tract dyskinesia, esophageal spasm, gastric atony, aerophagy, chronic hepatitis, chronic pancreatitis, *etc.*), cardiovascular system diseases caused by stress (*e.g.* essential hypertension, arrhythmia, (neurological) angina pectoris, essential hypotension, orthostatic dysregulation, myocardial infarction, arteriosclerosis, vertigo *etc.*), uropathy-reproductive system diseases caused by stress (*e.g.* dysuria, nervous pollakisuria (hyperreflexic bladder), nocturia, enuresis, psychogenic ischuria, impotentia, prostatism, urethral syndrome *etc.*), gynecologic disorder caused by stress (*e.g.* menopausal disorder, menstrual pain, premenstrual syndrome, infertility, frigidity, serious vomiting of pregnancy, abortion, immature birth, *etc.*), endocrine and metabolic disease caused by stress (*e.g.* anorexia nervosa, eating disorder, anorexia, hyperphagia, Bartter's syndrome, hyperthyroidism, glucose metabolism disorder (*e.g.* diabetes, (reflex) hypoglycemia *etc.*), lipid metabolism disorder (*e.g.* hyperlipemia *etc.*), gout, osteoporosis, hypothalamus disease, pituitary gland disease, accessory thyroid gland disease, adrenal cortex/adrenal medulla disease, gonad disease, psychogenic polydipsia, adiposity and so on), ophthalmologic diseases caused by stress (*e.g.* asthenopia, central retinitis, floaters, blepharospasm, primary glaucoma, vertigo *etc.*), otolaryngological

diseases caused by stress (*e.g.* tinnitus, vertigo, psychogenic deafness, chronic sinusitis, allergic rhinitis, smell disorder, stuttering, aphonia, *etc.*), dental surgery and dentistry caused by stress (*e.g.* temporomandibular arthrosis, glossopharyngeal neuralgia, sudden glossodynia, stomatitis, toothache, ozostomia, abnormal salivation, bruxism *etc.*),

5 surgical and orthopedic diseases caused by stress (*e.g.* postoperative abdominal neurosis, dumping syndrome, polysurgery, plastic postoperative neurosis, rheumatoid arthritis, low back pain, cervico-omo-brachial syndrome, stiff neck, fibrositis, polyarthralgia, systemic myalgia, gout, *etc.*), skin diseases caused by stress (*e.g.* chronic urticaria, atopic dermatitis, hyperhidrosis, eczema, skin pruritus, alopecia areata, *etc.*) and other

10 diseases caused by stress (*e.g.* cancer, systemic lupus erythematosus *etc.*).